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# Predicted Impact of Nicotine Reduction on Smokers with Affective Disorders

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## Abstract

**Objectives—**In 2009 the FDA acquired the authority to reduce the nicotine content in cigarettes if appropriate for public health, prompting research to evaluate the implications of this policy scientifically. Studies in non-psychiatric populations show that reducing the nicotine content of cigarettes to non-addictive levels reduces smoking rates and nicotine dependence. However, few studies have examined this hypothesis in vulnerable populations.

**Methods—**In this narrative review we examined the extant literature on the effects of nicotine reduction or cessation on symptoms of withdrawal, as well as psychiatric symptoms, among those with affective disorders.

**Results—**Following initial withdrawal from nicotine, smokers with affective disorders experience more severe mood disruption than smokers without these disorders. Use of very low nicotine content (VLNC) cigarettes during abstinence may help mitigate the mood-disrupting effects of initial abstinence. Once the initial effects of nicotine withdrawal on mood have passed, longer-term abstinence is associated with psychiatric improvement rather than worsening.

**Conclusions—**These findings suggest that if a national nicotine reduction policy were to be implemented, smokers with affective disorders would need additional support to overcome initial withdrawal but that long-term outcomes would likely be positive.

### Keywords

nicotine; affective disorders; depression; anxiety; PTSD; withdrawal; comorbidity

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**Human Subjects Statement**

This is a review of existing research studies and is not itself considered human research.

**Conflict of Interest Disclosure Statement**

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Affective disorders, a set of psychiatric disorders mainly comprised of mood disorders (eg, depressive disorders, bipolar disorder) and anxiety disorders (eg, generalized anxiety disorder, panic disorder and post-traumatic stress disorder) are prevalent among smokers. In the United States, 13% of smokers have a current mood disorder and 23% have a current anxiety disorder, compared to rates of 7% and 15% for these disorders in the general population.[1] Similarly, smoking prevalence rates among individuals with mood disorders are 2- to 3-fold higher than those in the general population.[2–4] In addition, smokers with affective disorders are more likely to be nicotine dependent, initiate daily smoking earlier, and smoke more cigarettes per day than those without psychiatric comorbidity.[5–9] As a result, affective disorders are associated with disproportionately-high rates of cardiovascular disease and tobacco-related cancers. [10–13] Effective methods of reducing tobacco dependence in this population are urgently needed.

Epidemiological data show that people with affective disorders are significantly less likely to quit smoking than those without current mental illness. [2,4,14] Smokers with affective disorders do not appear to differ from smokers without these disorders on readiness to quit,[15–17] nor are those with comorbid depression or anxiety disorders less likely to accept smoking cessation treatment when treatment is offered.[18–20] However, having a history of depression or anxiety reduces the likelihood of maintaining long-term abstinence.[21,22] In part, this may be due to higher nicotine dependence severity. [7,8] Moreover, smokers with affective disorders have difficulty accessing effective smoking treatments, in part, because of concerns among mental health clinicians that smoking cessation might destabilize psychiatric functioning.[23] The American Psychiatric Association and the US Department of Health and Human Services have published guidelines and statements to encourage mental health clinicians to assess smoking in their patients and assist them with quitting,[24–26] but adherence to these recommendations remains frustratingly low.[27]

A regulatory approach to treating tobacco dependence in the US may offer a novel avenue toward reducing cigarette smoking in people with psychiatric disorders. The 2009 enactment of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) gave the Food and Drug Administration (FDA) the authority to regulate tobacco products as appropriate to protect public health, including limiting the nicotine content of cigarettes. [28] A mandated reduction in the nicotine content of cigarettes to a non-addictive level could reduce tobacco reinforcement and dependence, making it easier for smokers to quit.[29–31] A nicotine reduction regulatory approach could be particularly beneficial to those who have less access to and success with currently-available smoking cessation treatments, such as people with affective disorders. However, one concern about a nicotine reduction policy is that it may have unintended negative consequences for these smokers. For example, if smokers with affective disorders are highly sensitive to the disrupting effects of nicotine reduction on mood or psychiatric symptoms, they could respond by increasing their smoking rate or altering their smoke inhalation patterns in an attempt to overcome these effects. Before going forward with a nicotine reduction strategy, it is important to assess the potential severity and persistence of these negative consequences in comorbid smokers, and to determine what strategies could be implemented to ameliorate these potential negative effects.

## METHODS

In this narrative review we examine the extant literature on the effects of reduction or cessation of nicotine on symptoms of withdrawal, as well as psychiatric symptoms among those with affective disorders. Of the diagnoses that generally have been included under affective disorders, relevant literature on those with depression, panic disorder, generalized anxiety disorder, and post-traumatic stress disorder (PTSD) was identified. This review focuses on those with a current diagnosis and papers referenced can be assumed to relate to current diagnoses unless specifically stated otherwise.

## RESULTS

### Effects of Reduced Nicotine Cigarettes on Withdrawal and Mood Symptoms

One way to predict the potential effects of a reduction policy on those with affective disorders is to examine the effects of very low nicotine content (VLNC; ie, .05 mg nicotine yield, also referred to as denicotinized) cigarettes on mood symptoms in these smokers. Numerous studies have examined the subjective, behavioral and physiological effects of acute and extended use of VLNC cigarettes in non-psychiatric populations. Results from these studies indicate that VLNC cigarettes substitute for usual-brand cigarettes under acute conditions, reducing cigarette craving, withdrawal symptoms and usual-brand cigarette use.[32–39] When smoked over a period of weeks to months, VLNC cigarettes continue to suppress cigarette craving while smoking rates and biomarkers of tobacco consumption decline.[40–42] These studies also have found that switching to VLNC cigarettes has little impact on mood or depression symptoms.[40,41]

Few studies have examined responses to VLNC cigarettes in people with affective disorders. One study compared acute effects of nicotine and denicotinized cigarettes on mood in smokers varying in current and past depression while they underwent positive or negative mood induction.[43] During positive mood induction, those with current depression experienced similar increases in positive mood whether smoking either a nicotine-containing or a VLNC cigarette, although the VLNC cigarette was somewhat less effective at dispelling negative mood. During negative mood induction, nicotine-containing cigarettes increased negative mood to a greater extent than did VLNC cigarettes. Another study compared responses to nicotine and VLNC cigarettes under neutral and negative mood induction procedures in smokers varying in depression history, and found that smokers with a history of depression smoked more puffs under all conditions, suggesting that they experience stronger reinforcing effects of smoking.[44]

Similar results have been reported when studying the effects of denicotinized cigarettes in those with PTSD. One study that investigated the effects of nicotine-containing and denicotinized cigarettes on trauma script-induced cigarette craving, affect, and PTSD symptoms in smokers with and without PTSD found that smoking either type of cigarette decreased negative affect in both groups.[45] In another comparison, smokers with PTSD experienced greater startle response after the presentation of a personalized trauma script when smoking a nicotine-containing cigarette than when smoking a denicotinized cigarette, suggesting that nicotine may exacerbate rather than reduce this stress response.[46]

Overall, these studies suggest that the positive and negative reinforcing effects of VLNC cigarettes are similar to those of nicotine-containing cigarettes when used acutely and do not exacerbate depression or anxiety symptoms in people with affective disorders; in fact, they suggest that substitution of VLNC for usual-brand cigarettes may reduce symptoms in some situations. However, to our knowledge, effects of extended-duration substitution of VLNC cigarettes for usual-brand cigarettes on psychiatric symptoms in smokers with affective disorders have not yet been reported.

## Effects of Smoking Cessation Treatment on Withdrawal and Symptoms of Anxiety or Depression

Another way of predicting how people with affective disorders may respond to a nicotine reduction policy is to examine the effects of smoking abstinence on withdrawal and psychiatric symptoms in these smokers. One area of potential concern following implementation of a reduction policy would be the effects on withdrawal-related negative affect among those with mood disorders. If smokers with mood disorders experience greater withdrawal symptom severity following nicotine reduction, there could be unintended negative consequences such as compensatory smoking. Indeed, there is some evidence to support greater effects on withdrawal in those with mood disorders. Smokers with current or past depressive disorders report more severe and prolonged nicotine withdrawal symptoms during a quit attempt compared to those without mood disorders,[47–49] particularly among women.[49,50] Regardless of sex, smokers with a history of major depression are 2.5 times more likely than those without depression to report relapse to smoking due to withdrawal. [51]

Likewise, several observational studies show that individuals with current or past anxiety disorders experience more frequent and severe withdrawal symptoms following smoking cessation compared to those without an anxiety disorder.[22,47,49,52–54] For example, a secondary analysis of outcome moderators from a large smoking cessation pharmacotherapy trial found that smokers with a history of panic, social anxiety or generalized anxiety disorders had higher negative affect and withdrawal symptoms before and on their quit day than smokers without these disorders.[53]

There is conflicting data on the relationship among anxiety disorders, withdrawal, and relapse, with one study finding that nicotine withdrawal is unrelated to resumed smoking following a quit attempt, whereas another showed that nicotine withdrawal and dependence fully mediated the relationship between nonspecific psychological distress (assessed via the Kessler K6) and continued smoking.[47,54] Among smokers with a history of PTSD, women are almost 5 times more likely than men to report that they relapsed to smoking due to nicotine withdrawal symptoms.[51]

After initial abstinence is achieved, there are concerns that smokers with affective disorders may experience prolonged mood disruption compared to smokers without these disorders. Indeed, some smoking cessation studies have noted that, among those with current or past depression, abstinence is associated with depression recurrence or worsening. [55–57] However, the majority have found that abstinence is associated with either no change or an improvement in depression symptoms.[58–67] In fact, one meta-analysis concluded that successful cessation appears to be associated with improvements in mood and psychological

quality of life, compared with continuing to smoke, even among those with psychiatric disorders.[68] However, subgroups of depressed smokers who do experience symptom worsening during initial abstinence have poorer cessation outcomes[69] and might benefit from nicotine replacement therapy, which has been found to offset some symptoms.[70]

Fewer smoking cessation studies have assessed associations between abstinence and psychiatric symptoms in smokers with anxiety disorders. Longitudinal data suggest that among those with a history of an anxiety disorder, quitting is associated with a decreased likelihood that anxiety symptoms will persist or recur.[71] Similarly, smoking cessation does not appear to be associated with exacerbations of trauma symptoms in people with PTSD, but rather, with symptom improvement. One observational study used Ecological Momentary Assessment techniques to assess changes in PTSD symptoms during a quit attempt and showed that relative to levels observed before quitting, PTSD symptoms were significantly lower and more stable during abstinence.[72] Both a pilot and larger smoking cessation study in individuals with PTSD found no significant differences in PTSD symptoms as a function of quitting, with both quitters and non-quitters reporting symptom improvements over 18 months.[73,74] In fact, non-quitters had slight increases in depression throughout the study, compared to quitters who had stable depression scores.[74]

Overall, results from smoking treatment studies suggest that although smokers with affective disorders appear to experience more severe initial withdrawal symptoms, long-term abstinence is not associated with prolonged worsening of negative mood or other psychiatric symptoms. However, because treatment studies do not control abstinence experimentally, it is difficult to determine the direction of causality between abstinence and psychiatric symptoms in these studies. Furthermore, treatment studies may underestimate effects of abstinence on psychiatric symptom worsening because smokers with affective disorders have a lower likelihood of achieving abstinence.[21,22,75] Studies that experimentally control abstinence to examine its effects on psychiatric symptoms in people with affective disorders could help clarify the direction of causality in these associations.

## Effects of Smoking Abstinence on Withdrawal and Symptoms of Anxiety or Depression in Experimental Studies

Laboratory studies that compare the effects of smoking abstinence on withdrawal and mood symptoms in smokers with and without affective disorders could provide much-needed insight into whether those with affective disorders may experience more severe and prolonged dysfunction from a nicotine reduction policy. Similar to the evidence from smoking cessation studies, laboratory studies show that smokers with depression experience more severe withdrawal symptoms during acute abstinence than non-psychiatric smokers. For example, one study found that women with a history of depression had higher levels of withdrawal symptoms and cigarette craving over a 3-day abstinence period than women without this history.[50] A subsequent study reported that those with elevated depression symptoms at baseline had higher cigarette craving, anxiety, difficulty concentrating, restlessness, and appetite during a 3-day period of abstinence.[76]

Likewise, experimental studies have found that smokers with anxiety disorders or high anxiety sensitivity have higher levels of negative affect and cigarette craving during

abstinence than smokers without these disorders,[52,77] although these findings have not been shown consistently.[78] Data specifically from those with PTSD show a similar pattern. Feldner et al[79] found that smokers with PTSD had more severe withdrawal symptoms during 12-hour abstinence than smokers without PTSD, and that withdrawal symptom severity mediated the relationship between diagnosis and panic symptoms during a hyperventilation challenge. Another study comparing the effects of 12-hour smoking abstinence and reinstatement on nicotine withdrawal symptoms in smokers with and without PTSD found that those with PTSD had less relief from craving and negative affect when they resumed smoking.[80] Furthermore, in smokers with and without PTSD, nicotine-containing cigarettes were more effective at relieving craving and withdrawal than denicotinized cigarettes.

A few studies also have examined effects of experimentally- induced abstinence on anxiety symptoms, specifically, among smokers with PTSD. One study, in smokers who had endorsed a DSM-IV- TR-defined PTSD Criterion A traumatic event, found that those with higher PTSD symptoms at baseline had higher anxiety levels during a smoke-as- usual condition, but not following 12-hour abstinence. [81] A study comparing anxiety levels during a biological challenge after 12-hour abstinence found that persons with a current panic disorder responded similarly to those who did not.[82]

Overall, experimental studies generally find that smokers with affective disorders are more sensitive to the effects of abstinence on withdrawal symptoms. However, those with anxiety disorders do not appear to have disproportionate increases in anxiety symptoms during abstinence. Surprisingly few experimental studies of this type have been conducted, though, and few studies have examined effects of abstinence of durations greater than 12 hours.

## Effects of Nicotine Abstinence in Preclinical Models of Affective Disorders

Another way to predict the potential effects of nicotine reduction on affective disorders is by reviewing the evidence from the preclinical literature. Animal models are useful for examining longer abstinence durations, determining causality, and illuminating mechanisms underlying behavioral changes. Most relevant to this paper are studies on the effects of abstinence from chronic nicotine on rodent behaviors thought to be analogous to symptoms of depression and anxiety in humans. Indeed, there is a fairly extensive literature on modeling nicotine withdrawal-induced depression in preclinical models.

An increase in behaviors considered analogous to human depressive symptoms (eg, immobility during stressful events, increased food consumption, decreased social interaction, lack of responsiveness to positive stimuli) following discontinuation of chronic nicotine is a common finding in rodent studies.[83] This increase in symptoms is so common that it has spawned a host of studies looking for possible treatments of withdrawal-induced depression.[84–87] Furthermore, the shared neurobiological substrates of nicotine withdrawal and depression, as well as the responsiveness of nicotine withdrawal symptoms to antidepressants, suggest that the 2 phenomena are similar.[88] Indeed, anhedonia caused by nicotine withdrawal is suggested as a good model on which to test novel treatments for depression. Nicotine has been suggested even as a potential treatment for depression.[89] Despite the ubiquitous effect of nicotine withdrawal on depressive symptoms, there is

evidence that certain populations, such as women, may be especially prone to such effects.[90,91] Overall, the preclinical literature clearly shows that withdrawal from chronic nicotine causes behaviors analogous to symptoms of depression.

Researchers also have employed animal models to explore the relationship between nicotine and symptoms of anxiety.[83] As smokers often report smoking to reduce anxiety symptoms, the use of animal models should help clarify the anxiolytic or anxiogenic effects of nicotine administration and withdrawal. In animal models, anxiety is often characterized by measuring behavioral responses to situations that are thought to be analogous to human anxiety, such as exploring unfamiliar areas and anticipation of stressful events.[83] Several tasks are used to this end, with some of the most common being the social interaction task, the elevated plus maze, fear-potentiated startle, light-dark exploration, the mirror chamber and the marble burying task.[92–94]

Given the variety of tasks involved and the multitude of methods of administration, it is not surprising that the resulting literature is difficult to interpret. The effects of nicotine exposure can be anxiogenic or anxiolytic depending on a host of factors including dose, base rate of anxiety behavior, rodent strain, task, and housing condition.[93,95,96] As with depressive symptoms, sex also moderates the effects of nicotine on anxiety-like behaviors, with anxiogenic effects of chronic nicotine manifesting for women but not men in some experiments.[97]

Given the inconsistent effects of nicotine exposure on anxiety, it is not surprising that the literature on nicotine withdrawal is also complex. Generally, chronic nicotine in animal models results in anxiogenic effects during withdrawal. [93,98] However the effect is not consistent, as effects of withdrawal can vary based on strain of rodent and may require highly stressful testing situations to manifest.[98] Effects also can vary by age,[99] strain,[95] task,[100] and phenotype.[101] Given the variability of the effects of chronic nicotine and nicotine withdrawal, neither a decrease nor an increase in anxiety symptoms following a decrease in nicotine levels in cigarettes could be predicted based upon current literature.

Given the possibility of a nicotine reduction policy, developing relevant preclinical models to explore potential implications of this policy are warranted. Indeed, a line of preclinical research is underway to examine variables that may moderate the effects of nicotine reduction in humans.[102] For example, Smith et al[103] maintained rodents on a high dose of nicotine, then compared the effects of gradual versus immediate reduction in nicotine dose on nicotine-maintained responding, and found that both decreased nicotine self-administration to a similar extent. Smith et al[104] also modeled how a nicotine reduction policy might affect established versus naive tobacco users. Rodents acquired self-administration of either higher or lower nicotine doses, and then self-administration of the low dose was assessed. Those who had acquired self-administration with the lower dose maintained lower levels of nicotine-reinforced behavior than those who had acquired self-administration with the higher dose, suggesting that lowering the nicotine content of cigarettes may reduce the acquisition of tobacco dependence. These self-administration models could be used in combination with animal models of affective disorders (eg, learned helplessness) to examine potential effects of a nicotine reduction policy on those with

affective disorders. For example, such studies could compare rodents varying in depression-like behaviors on sensitivity to nicotine dose reduction, acquisition of nicotine-maintained behavior, and behavioral responses to gradual versus immediate nicotine reduction.

## DISCUSSION

Given the high proportion of smokers with affective disorders, and their lower cessation rates, a national policy of nicotine reduction may be the most effective avenue toward reducing tobacco-related morbidity and mortality in people with these disorders. Relevant human and preclinical studies indicate that during initial abstinence, people with affective disorders experience more severe and prolonged withdrawal-related negative mood than people without affective disorders; moreover, women with mood disorders are particularly vulnerable to experiencing these effects (Table 1). These findings suggest that if a national nicotine reduction policy were to be implemented, smokers with affective disorders might experience more severe mood disruption than smokers without these disorders, at least initially. However, results from acute laboratory studies of VLNC cigarettes in smokers with affective disorders also indicate that, presumably by providing the sensorimotor cues associated with smoking, use of VLNC cigarettes during abstinence helps to mitigate the mood-disrupting effects of initial abstinence. Moreover, the weight of the evidence from smoking treatment studies suggests that once the initial effects of nicotine withdrawal on mood have passed, longer-term abstinence is associated with psychiatric improvement rather than worsening. However, several important questions remain that could be addressed with human and preclinical experimental studies.

First, although cessation studies largely indicate that extended-duration abstinence is associated with psychiatric improvement rather than worsening, the direction of causality in this relationship cannot be determined because these studies do not experimentally-control abstinence. One experimental study that provides a model for examining whether abstinence improves psychiatric symptoms used high-value, abstinence-contingent reinforcement to investigate the effects of 3-day abstinence on mood, craving, psychiatric symptoms and nicotine reinforcement in smokers with schizophrenia.[105] Similarly-designed studies, but with a longer abstinence duration, would be useful for examining the effects of extended-duration abstinence, with and without VLNC cigarettes, on psychiatric symptoms in people with affective disorders. Comparisons of VLNC smoking topography among smokers with and without affective disorders will be important to examine whether smokers with affective disorders may try to compensate for perceived reductions in nicotine content by smoking VLNC cigarettes more intensely, and if so, how long these topography adjustments last, and to what extent they affect biomarkers of tobacco exposure.

Second, and related to the above point, it is important to determine how any negative effects of nicotine reduction in smokers with affective disorders might be mitigated. Among non-psychiatric smokers, use of transdermal nicotine during VLNC cigarette use has had inconsistent effects on withdrawal symptoms, but results generally favor its use.[31,106] Electronic cigarettes, which provide nicotine without the combustion products of conventional cigarettes, are another product that could be used to mitigate any negative consequences of nicotine reduction. Several features of electronic cigarettes, such as their

rapid onset of action, intermittent dosing, and behavioral component, may make them more effective substitutes for cigarettes than transdermal nicotine. Another potential complement to VLNC cigarettes could be a pharmacotherapy such as bupropion, an antidepressant medication that inhibits the reuptake of norepinephrine and dopamine and antagonizes α3β2 and α4β2 nicotinic acetylcholine receptors[107] or varenicline, a partial agonist at α4β2 and full agonist at α7 nAChRs.[108] These medications reduce withdrawal-related negative affect among smokers without psychiatric disorders[109–111] and reduce smoking without worsening depression or anxiety symptoms among smokers with current or past major depression.[112,113] Moreover, these approaches could be combined with cognitive-behavioral therapies such as behavioral activation therapy, which has been found to reduce both smoking and depression among smokers with elevated depression symptoms.[114]

Third, an important question is whether a reduction in the nicotine content of cigarettes should be implemented abruptly or gradually over time. An immediate reduction in nicotine content would have a more rapid benefit on public health, but a gradual reduction might be less disruptive for smokers in general, and for smokers with psychiatric disorders in particular. Studies are underway that examine the effects of these reduction approaches on smoking, biomarkers of tobacco-related disease, and psychiatric symptoms in people with affective disorders; however, it will be several years before results of these studies are known. Recently, a study using a rodent model found that both immediate and gradual reduction approaches produced similar decreases in nicotine-maintained behavior.[103] This preclinical line of research complements human experimental studies of VLNC cigarettes. Whereas animal models cannot replicate the full range of symptoms and deficits associated with affective disorders, animal models that produce some depression-like symptoms may be useful for predicting what the effects of nicotine reduction might be on both nicotine-maintained behavior and behaviors thought to be indicative of human depression and anxiety symptoms.[102]

Notwithstanding any concerns expressed in this paper about how nicotine reduction may affect psychiatric symptoms in people with affective disorders, it is important to balance such concerns against the enormous potential benefit of nicotine reduction on the health of these and all smokers. Our intention in raising these concerns is to promote research that will examine how any unintended negative consequences of nicotine regulation might be mitigated, not to undermine an important effort that has the potential to make dramatic improvement in public health.[115] Available research to date suggests that the negative consequences of nicotine reduction may be short-lived; moreover, these consequences may be reduced through public education efforts and pharmacological and cognitive- behavioral support.

## IMPLICATIONS FOR TOBACCO REGULATION

The findings of this review suggest several implications for researchers, clinicians, and policymakers before and during a nicotine-reduction policy. First, researchers need to expand the literature on the effects of VLNC cigarettes, especially in vulnerable populations. Whereas it is clear that initial smoking abstinence is associated with a worsening of affective symptoms among those with anxiety or depression, it is less clear what the effects of

switching to VLNC cigarettes would be in this population. Researchers could test whether smoking VLNC cigarettes ameliorate withdrawal-related increases in affective symptoms. If so, then a nicotine-reduction policy could be less disruptive than might be suggested from this review. Additionally, researchers could test the effectiveness of methods to ameliorate withdrawal-related increases in affective symptoms, such as the use of nicotine from other sources (eg, NRT, e-cigarettes) or other pharmacotherapy (eg, bupropion or varenicline). A third potential area for further research would be to examine whether a nicotine reduction policy should be implemented in an abrupt or gradual manner, given the potential effects on vulnerable populations. As mentioned above, a combination of studies in humans with affective disorders and animal models of depression and anxiety could inform policy about which type of transition would be least disruptive.

Additionally, if a nicotine-reduction policy is implemented, clinicians should be made aware of potential effects on those with affective disorders and prepared to offer additional support (eg, counseling, NRT) to their patients. Policymakers should be cognizant of the potential short-term negative consequences of a nicotine-reduction policy, but should balance those against the probable long-term benefits of this policy to these and other smokers.

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## Table 1

Summary of Findings

| | Reduced-nicotine content cigarettes | Smoking cessation | Laboratory studies | Preclinical models |
|---|---|---|---|---|
| **Depression** | No increases in negative affect following reduced nicotine content cigarette use[43,44] | More severe and prolonged nicotine withdrawal symptoms following prolonged abstinence[47–51] Long-term effects on changes in depression are mixed[55–67] | More severe craving and withdrawal symptoms following brief abstinence[50,76] | Increase in depressive-like symptoms following discontinuation of chronic nicotine[83–87] |
| **Anxiety/PTSD** | No increases in negative affect following reduced nicotine content cigarette use[45,46] | More frequent and severe nicotine withdrawal symptoms following prolonged abstinence [22,47,49,52–54] No change or decreases in anxiety/PTSD symptoms[71–74] | More severe craving and withdrawal symptoms following brief abstinence[52, 77,79,80] No changes in anxiety following brief abstinence[81,82] | No consistent effect on anxiety-like symptoms following discontinuation of chronic nicotine[93–101] |