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Are Smoking Cessation Treatments Associated with Suicidality Risk? An Overview

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ABSTRACT: Risk of suicidality during smoking cessation treatment is an important, but often overlooked, aspect of nicotine addiction research and treatment. We explore the relationship between smoking cessation interventions and suicidality and explore common treatments, their associated risks, and effectiveness in promoting smoking reduction and abstinence. Although active smokers have been reported to have twofold to threefold increased risk of suicidality when compared to nonsmokers,¹⁻⁴ research regarding the safest way to stop smoking does not always provide clear guidelines for practitioners wishing to advise their patients regarding smoking cessation strategies. In this article, we review pharmacological and cognitive behavioral therapy (CBT) options that are available for people seeking to quit smoking, focusing on the relationship between the ability of these therapies to reduce smoking behavior and promote abstinence and suicidality risks as assessed by reported suicidality on validated measures, reports of suicidal ideation, behaviors, actual attempts, or completed suicides. Pharmacotherapies such as varenicline, bupropion, and nicotine replacement, and CBTs, including contextual CBT interventions, have been found to help reduce smoking rates and promote and maintain abstinence. Suicidality risks, while present when trying to quit smoking, do not appear to demonstrate a consistent or significant rise associated with use of any particular smoking cessation pharmacotherapy or CBT/contextual CBT intervention reviewed.

KEYWORDS: nicotine dependence, smoking, smoking cessation, suicidality

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Introduction

There is a demonstrated increased risk of reported suicidal thoughts or behaviors in active or daily smokers compared to those who have never smoked.^{2,4-7} *Suicidality* is a general term that refers to a variety of behaviors, including suicidal ideation, suicide attempts, and successful completion of suicide.¹ We use the term suicidality in this manuscript to refer to any of these events. Suicidality can be assessed by using standardized measures, self-report of behaviors, or other documentation of ideation, behaviors, attempts, or completed suicide. People who smoke have a twofold to threefold increased risk of suicide.^{3,4}

The link between active smoking and increased suicidal risk, although strong and reliable, is still not well understood and is explored in detail in other reviews (eg, Hughes¹). Our primary focus is on increased risk of suicidality during smoking cessation, and thus, we will only briefly mention the proposed associations between active smoking and suicidality. Active smoking may be associated with increased suicide risk

due to shared confounding variables that are correlated with both suicide and smoking, including mood symptoms such as depression, anxiety, and emotional lability.⁸ The underlying mechanism for this increased risk is unclear, although confounding by alcohol misuse and mental illness seems to explain some, but certainly not all, of the association.¹ Two epidemiological studies support a direct positive relationship between smoking/nicotine dependence and suicide after controlling for a number of possible confounding mental health disorders.^{9,10} The first of these studies⁹ found that nicotine dependence was one of only four diagnoses that independently accounted for a high proportion of suicide attempts (the other three disorders were major depressive disorder, borderline personality disorder, and post-traumatic stress disorder). The second study¹⁰ found that nicotine dependence was associated with suicide attempts, independent of all Axis I and Axis II conditions as well as physical diseases. Additionally, Yaworski et al.¹⁰ recently found that previously nicotine-dependent individuals who have abstained for at least one year



were significantly less likely to attempt suicide than people still dependent on nicotine, which suggests a direct role of nicotine dependence on suicidality. Kendler et al.¹¹ have also produced research demonstrating shared genes that contribute to increased likelihood of both smoking and depression. Smoking leads to a physical dependence on nicotine and often causes serious physical illnesses, which has also been hypothesized to lead to an increased risk of suicide.¹² Once addicted, an individual's attempts to quit smoking, in the face of serious illness or otherwise, can result in withdrawal symptoms, including irritability, headaches, weight gain, and insomnia.¹³ Nicotine withdrawal symptoms may also be accompanied by depressed mood in some individuals.¹⁴ The risk of suicide is increased by the presence of psychological factors such as depression, anxiety, emotional instability, and antisocial personality.¹⁵ Some have hypothesized that quitting smoking may precipitate depression, which may increase the risk of suicide.¹⁶ Because risk factors tend to overlap, smoking may be conceptualized as a way of *self-medicating* to abate these symptoms.¹⁷ Nicotine has been demonstrated to help regulate mood and reduce negative effects that may reduce anxious and impulsive symptoms, thus potentially reducing suicidality risks.¹⁸ Smoking cessation may also contribute to suicide risk because an important coping mechanism (ie, smoking) is removed. Definitive causal links are challenging to make because many of the risk factors for suicide are associated with risk factors for smoking.^{12,19}

The link between various forms of medications to help quit smoking and increased suicidality risk is equally confounding. Part of the challenge is that there are multiple interventions available to aid with smoking cessation, and they work in differing ways. Pharmacological options include bupropion, varenicline, and various forms of nicotine replacement therapy. Some of the pharmacotherapies may carry an increased risk of suicide,²⁰ although not all of the research supports this.²¹ Nonpharmacological approaches include cognitive and/or behavioral therapy (referred to also as behavioral psychotherapy) and approaches involving mindfulness training. Cognitive behavioral therapies have been shown to increase success rates and may mitigate suicide risk during smoking cessation.²² In this paper, we review both the suicide risks associated with and the effectiveness of nicotine replacement therapies, other commonly prescribed smoking cessation pharmacotherapies, cognitive behavioral psychotherapies, and mindfulness strategies.

Methods

We obtained information by searching Ovid and PubMed for articles related to smoking cessation and suicidality. Specific terms included smoking cessation, nicotine dependence, varenicline, bupropion, nicotine replacement, cognitive behavioral therapy, mindfulness, and contextual cognitive behavioral therapy, each crossed with suicide, suicidality, and suicidal ideation. We then selected specific manuscripts based

on the appropriateness and applicability of each to the topic. We focused on smoking cessation treatment in people who are actively smoking and did not include relapse prevention studies or purely educational programs. Additional manuscripts were obtained from appropriate references cited in these manuscripts as well as references in the public domain obtained from pharmaceutical companies and regulatory agencies. A total of ~100 manuscripts were reviewed and information from 92 was included in this review based upon the authors' judgments.

Pharmacotherapies for Smoking Cessation

Pharmacotherapy for smoking cessation primarily targets reducing nicotine withdrawal symptoms and cravings in order to help people stop smoking. Nicotine withdrawal symptoms experienced by smokers include headache, nausea, anxiety, depression, and many other psychological and physiological discomforts.¹³ The general mechanisms of drug therapies for smoking cessation work by blocking nicotine from binding to its receptor and enhancing the release of neurotransmitters.²³ Some medications such as varenicline and nicotine replacement medications may also have an agonistic effect.^{24,25} The inhibition of nicotine aids in alleviating withdrawal symptoms and cravings as the reinforcing effects of nicotine are diminished.²⁰ Although many have reported success in significantly reducing tobacco consumption or quitting smoking with pharmacological therapies such as bupropion and varenicline, these medications can have side effects, and there is some support that they may increase depressive symptoms and/or risk for suicidality, which must be considered when prescribing.^{26,27}

The potential increased risk of suicidality observed in some reports of pharmacotherapies for smoking cessation is a concern. In 2009, the US Food and Drug Association added warning labels on manufactured smoking aids alerting a possible association between suicidal behaviors and the usage of bupropion and varenicline.²⁸ The warning highlighted an increased risk of psychiatric symptoms such as agitation, hostility, depressed mood, and most importantly, increased occurrences of suicidal behaviors. Observed in the post-marketing reports, patients with no history of psychiatric disorders reported suicidal thoughts and an increase of suicidal ideation and behaviors after using these products.²⁸ When recommending prescription drugs for addiction treatment, it is vital to weigh the possible adverse or even potentially life-threatening effects against the potential benefits to ensure the health and safety of the patient. We review the predominant types of smoking cessation pharmacotherapies currently researched: nicotine replacement therapies, bupropion, and varenicline.

Nicotine replacement therapies. Nicotine replacement therapies (NRTs) are licensed as first-line treatments for smoking cessation both in the United States and Europe.²⁹ NRT was the first effective pharmacotherapy for



treatment of nicotine dependence and is currently available without a medical prescription. It is marketed as a transdermal patch in various dosages, which provides slow absorption through the skin, or as a nasal/buccal absorption product (chewing gum, lozenges, sublingual tablets, nasal sprays, and inhalers).^{20,29}

NRTs help people quit smoking by reducing the cravings to smoke and both the physiological and psychological withdrawal symptoms that can be experienced during and after quitting. NRTs have also been shown to reduce the reinforcing effects of smoking.²⁰ A 2013 Cochrane review, covering 267 studies and involving 101,804 participants who explored multiple pharmacotherapies for smoking cessation, found NRT to be superior to placebo, helping ~80% more people to quit than placebo (odds ratios (ORs) of 1.84 (95% CrdI 1.71–1.99). In other words, for every 10 people who quit with placebo, ~18 were expected to quit with NRT.

Efficacy was defined as sustained abstinence at least six months after smoking cessation. In head-to-head comparisons, individual NRTs were equally effective among the different formulations and also equally effective to bupropion. Varenicline was more effective for sustained smoking cessation than either bupropion or a single NRT, but equally effective when compared to combined NRTs.²⁹

Moore et al.²⁸ examined case reports of adverse events reported to the United States Food and Drug Administration (US FDA) for NRTs, varenicline, and bupropion for smoking cessation. The NRT group (including all routes of administration) was used as a comparison group for the varenicline and bupropion. An additional comparison group included combined case reports for three commonly used antibiotics. This antibiotic comparison group was established to assess the underlying risks that might be attributed to the smoking cessation population independent of study drugs, in a population not seeking to stop smoking. The main outcome measure was the ratio of reported suicide/self-injury or depression cases for each drug compared to all other serious events for that drug. The authors identified 3,249 reported cases of suicidal/self-injurious behavior or depression overall. They found a higher number of reports of suicidality/self-injurious behavior among patients using NRTs ($N=50$) compared to those using antibiotics ($N=21$). Of note, there were 40 cases of suicidal ideation, 2 attempts, 1 indication of suicidal behavior, 1 indication of intentional self-injury, 4 intentional overdoses, and 4 completed suicides in the NRT group. There were seven cases of suicidal ideation, seven attempts, zero indication of suicidal behavior, one indication of intentional self-injury, eight intentional overdoses, and three completed suicides in the comparison antibiotic medication group. Moore et al.²⁸ concluded that using NRTs for smoking cessation may be associated with higher risk of suicidality.²⁸ However, the evidence supporting their conclusion is somewhat limited, as they did not include a comparison group of individuals attempting to quit smoking without any pharmacotherapy. Additionally, both varenicline

and bupropion were observed to have far higher numbers of individuals who experienced suicidal ideation ($N=1135$ and $N=73$), attempts ($N=323$ and $N=56$), behaviors ($N=63$ and $N=1$), and completions ($N=272$ and $N=19$) than individuals who were taking NRTs.

Thomas et al.²¹ also compared the risk of suicide, self-harm, and depression in patients prescribed varenicline or bupropion with those prescribed nicotine replacement therapy in a prospective cohort study within the Clinical Practice Research Datalink. Outcomes were treated depression and fatal as well as non-fatal self-harm within three months of the first smoking cessation prescription. Hazard ratios or risk differences were estimated using Cox multivariate regression models, propensity score matching, and instrumental variable analysis. These researchers reported 92 cases of suicide and non-fatal self-harm and 1,094 records of treated depression at three months of follow-up after the date of treatment initiation. Six of these suicides were in the NRT group and two in the varenicline group. In contrast to the findings of Moore et al.²⁸, Thomas et al.²¹ found no evidence that patients prescribed varenicline had a higher risk of fatal or non-fatal self-harm (hazard ratio: 0.88; 95% confidence interval: 0.52–1.49) or treated depression (hazard ratio: 0.75; 95% confidence interval: 0.65–0.87) than patients prescribed NRTs and also demonstrated no evidence that patients prescribed bupropion had a higher risk of fatal or non-fatal self-harm (hazard ratio: 0.83; 95% confidence interval: 0.30–2.31) or treated depression (hazard ratio: 0.63; 95% confidence interval: 0.46–0.87) than patients prescribed NRTs. Thus, Thomas et al.²¹ concluded that their research did not support an increased risk of suicidality or depression in patients prescribed varenicline or bupropion versus NRTs. In fact, in their basic model, hazard ratios showed a lower risk of all-cause mortality (hazard ratio: 0.37; 95% confidence interval: 0.26–0.54) in patients prescribed varenicline than in those prescribed NRTs. Findings were similar for bupropion compared to NRT with self-harm, and suicide risks were lower in bupropion versus NRT (hazard ratio: 0.31; 95% confidence interval: 0.13–0.74) at three months. The results of Thomas et al.²¹ are limited by the fact that the study was an uncontrolled cohort study, and thus many variables, such as adherence, the use of other medications, and history, could not be controlled.

Overall, it would appear that the literature reviewed appears to support that NRTs used for smoking cessation do not increase rates of suicidality any greater than bupropion or varenicline and that NRTs may actually demonstrate lower risks in this population.

Bupropion SR. Bupropion SR was the first non-nicotinic pharmacotherapy approved for smoking cessation and was first licensed as an antidepressant. Bupropion is a tetrahydroisoquinoline derivative that preferentially blocks the reuptake of norepinephrine and dopamine in the mesolimbic system and the nucleus accumbens. Although its pharmacological



mechanism of action in smoking cessation remains unclear, data from animal studies suggest that it acts as an antagonist at the nicotinic acetylcholinergic receptor. Therefore, it may work by blocking the reinforcing effects of nicotine, decreasing withdrawal symptoms, and potentially reducing depressed mood and cigarette cravings. Given its stimulant properties and appetite suppression, bupropion has also been postulated as helpful in reducing post-smoking cessation weight gain.^{20,29,30} A 2014 Cochrane review, examining evidence up to July 2013, evaluated 44 clinical trials and concluded that there is a high-quality evidence base confirming the benefit of bupropion used as a single pharmacotherapy for smoking cessation. The effects were comparable across several different populations and settings, using different types of behavioral support, and in smokers regardless of past history of depression.³⁰ A previous review had found that, similar to NRTs, bupropion helped about 80% more smokers quit than placebo.²⁹

Several studies have examined the use of bupropion in specific populations that have higher risks associated with continued smoking. For example, Tonstad et al.³¹ found that more than twice as many smokers with cardiovascular disease who had been treated with bupropion SR for seven weeks had quit smoking at one year, compared with placebo; the safety profile was comparable to that observed in general smoking populations. Of note, depressed subjects were excluded for the trial, and worsening mood and/or depression were not specifically measured nor mentioned during the trial.³¹ In a small, double-blind pilot study of alcohol- and nicotine-dependent patients ($N = 11$), randomized to bupropion or placebo, patients in the bupropion arm had a significant reduction in smoking exposure and withdrawal symptoms.³² In a trial to assess smoking cessation among inner city African Americans, a group with likely higher rates of smoking and greater smoking-attributable morbidity and mortality, sustained smoking cessation rates (26 weeks) were significantly higher in patients taking bupropion for 7 weeks compared with placebo. There were no significant differences in neuropsychiatric adverse events between both groups.³³ Tashkin et al.^{34,99} conducted a double-blind, randomized, placebo-controlled trial of individuals with mild-to-moderate chronic obstructive pulmonary disease who were actively smoking. Abstinence rates were significantly higher in those receiving bupropion than in those receiving placebo, after week 4, during the 12-week treatment phase, and at the 6-month follow-up.

Post-marketing reports of neuropsychiatric effects (worsening depression and suicidality) led the FDA and the European Medicine Agency to add a *black box warning* to the labels of bupropion for smoking cessation (marketed as Zyban, Wellbutrin, and generics) in 2009.²⁰ This warning highlighted the risk of serious neuropsychiatric symptoms such as changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide.³⁵ In a study that analyzed the French Pharmacovigilance Database from 2001 to 2004 and included all spontaneous reports of

serious adverse reactions to bupropion, Beyens et al.³⁶ found that neuropsychiatric side effects like depression and suicide attempts were reported in a frequency similar to that of the general population (17.3% of the cases). The most frequently reported serious adverse events in the study were seizures, angioedema, and serum-like reactions.³⁶ It is important to note that this study included data from the first three years after the start of marketing of bupropion SR for smoking cessation and prior to the black box warning.

In their evaluation of case reports of adverse events reported to the FDA, Moore et al.²⁸ found that the odds ratio for suicide was elevated for bupropion compared to the antibiotic comparison group (OR: 12.5; CI: 9.1–17.2). They identified 229 cases (7%) of suicidal/self-injurious behavior or depression, 19 cases (6%) of completed suicides, and 56 cases (15%) of suicide attempts associated with bupropion.²⁸ These findings demonstrate less risk for suicidality in those prescribed bupropion versus those prescribed varenicline, and an increased risk for suicidality in those prescribed bupropion than for those patients receiving NRTs (as described in the NRT section).

However, a number of meta-analyses of randomized controlled trials (RCTs) have also explored the association of depression and suicidality with use of bupropion for smoking cessation, and found no correlation. Wightman et al.³⁷ analyzed data on antidepressant suicidality from RCTs using bupropion for multiple indications. The studies were conducted between 1976 and 2006, and no statistically significant differences were found between bupropion and placebo in terms of expressed suicidal ideation or behavior.³⁷ A 2013 Cochrane review, evaluating 82 trials, also demonstrated no excess of neuropsychiatric or cardiovascular events in those prescribed bupropion.²⁹ A 2014 Cochrane review specifically evaluating antidepressants for smoking cessation did not detect any difference between bupropion and placebo or no pharmacotherapy controls in rate of psychiatric or cardiovascular serious adverse events but detected a marginal and nonstatistically significant increased rate of serious adverse events in people randomized to bupropion.³⁰

Overall, findings reviewed support that bupropion appears to be effective for many in promoting smoking cessation and appears to have limited and mixed support regarding the increased risk of suicidality with its use. Based upon research reviewed, bupropion also has similar risk of suicidality to placebo or no treatment and may have lower risks for suicidality when compared to varenicline, but may have higher rates of risk than NRTs.

Varenicline. Varenicline, marketed as Chantix, is the most recently approved pharmacotherapy for smoking cessation.³⁸ It was derived from the cytisine compound and has greater bioavailability and selectivity for alpha-4 beta-2 nicotinic receptors as a partial agonist. It is completely absorbed orally, not affected by food, and reaches steady state within 4 days of administration; its half-life is 24 hours. It has low protein binding and,



unlike nicotine, does not undergo hepatic metabolism. Most of the drug is excreted unchanged in the urine.³⁹

As a partial agonist of the alpha-4 beta-2 nicotinic receptor, varenicline stimulates receptor-mediated activity, blocking the ability of nicotine to activate these receptors and stimulating dopamine turnover in the nucleus accumbens (involved in the reward circuit and addiction) by 32%–45% of that achieved with nicotine. This stimulation leads to a moderate and sustained increase in dopamine levels, thereby decreasing nicotine cravings and withdrawal symptoms present during smoking cessation. In those who relapse during treatment, varenicline also appears to reduce the rewards experienced by blocking nicotine-induced dopaminergic activation (antagonist action), which aids in abstinence.^{20,29,40,41}

In a Cochrane review covering a total of 267 studies (20 specific for varenicline), Cahill et al.²⁹ found that varenicline more than doubled the odds of quitting smoking versus placebo (ie, for any 10 individuals who quit with placebo, 28 could be expected to quit with varenicline). Head-to-head comparisons with other smoking cessation pharmacotherapies showed that varenicline was superior to single forms of NRT and also to bupropion; it was of equal efficacy to combination NRT.²⁹ Other meta-analyses have confirmed the increased efficacy of varenicline on smoking cessation rates during 12-week treatment compared with placebo and also bupropion.²⁰ In a large RCT examining bupropion SR, varenicline, and placebo for smoking cessation, it was found that the efficacy of varenicline in the short term and long term (up to 52 weeks) exceeded that of both placebo and bupropion SR.⁴¹

In November 2007, the US FDA first reported that varenicline might cause serious neuropsychiatric symptoms, adding information about the reported effects to the *post-marketing experience* section of the prescribing information and also requesting that the manufacturer include this information. In 2008, the US FDA issued a safety warning for healthcare professionals, advising that varenicline could have neuropsychiatric adverse events such as changes in behavior, agitation, suicidal ideation, and attempted and completed suicide. A black box warning for this medication was required starting in 2009, based on continued post-marketing adverse event reports for varenicline and bupropion.^{26,27,35,40,42,43}

Moore et al.²⁸ found that 90% of the 3,249 FDA-reported cases of suicidal/self-injurious behavior or depression associated with smoking cessation pharmacotherapies were found in individuals taking varenicline. This included 272 (92%) of the reported completed suicides and 323 (85%) of all reported suicide attempts. The authors concluded that varenicline is unsuitable for first-line use in smoking cessation. Ahmed et al.⁴⁰ analyzed 25 published case reports spanning from 2006, when varenicline received FDA approval, to 2012. Analysis of all reports using the Naranjo causality scale, a method for estimating the probability of adverse drug reactions, indicated probable causality in 76% of the cases and definite causality in 12% of the cases.

Prospective cohort studies have been performed in the UK without evidence that varenicline was associated with increased risk of serious neuropsychiatric adverse events. A cohort study including 80,660 adults who were prescribed NRT, varenicline, or bupropion between 2006 and 2008 found no clear evidence that varenicline was associated with an increased risk of fatal or nonfatal self-harm or of depression.⁴⁴ Thomas et al.²¹ identified 119,546 adults prescribed pharmacotherapy (varenicline, bupropion, NRT) for smoking cessation in primary care practices between 2006 and 2011. They found no evidence of increased risk of suicidal behavior in patients prescribed varenicline or bupropion compared to those prescribed NRT. Additionally, Tonstad et al.⁴⁵ in a pooled analysis examined the incidence of psychiatric adverse events in 10 completed RCTs of varenicline and that the incidence of psychiatric disorders other than sleep disorders and disturbances was 10.7% in subjects treated with varenicline and 9.7% in subjects treated with placebo, with an RR of 1.02 (95% CI: 0.86, 1.22). The RRs (95% CI) versus placebo of psychiatric adverse events with an incidence $\geq 1\%$ in the varenicline group were 0.86 (0.67, 1.12) for anxiety disorders and symptoms, 0.76 (0.42, 1.39) for changes in physical activity, 1.42 (0.96, 2.08) for depressed mood disorders and disturbances, 1.21 (0.79, 1.83) for mood disorders and disturbances not elsewhere classified, and 1.70 (1.50, 1.92) for sleep disorders and disturbances. The authors reported no cases of suicidal ideation or behavior in varenicline-treated subjects in the 10 placebo-controlled studies analyzed. However, among three trials that were excluded from the analysis because of their open-label design, two cases of suicidal ideation and one completed suicide were reported in patients who had been treated with varenicline. There was no evidence of dose responsivity except for the sleep disturbances.⁴⁵

A UK study⁴⁴ examined the association of varenicline and increased risk of suicide and suicidal behavior compared to bupropion and NRT in a cohort study nested in the General Practice Research Database. Gunnell et al.⁴⁴ found no clear evidence that varenicline was associated with an increased risk of fatal ($n = 2$) or non-fatal ($n = 166$) self-harm, although a twofold increased risk cannot be ruled out on the basis of the upper limit of the 95% CI. Compared with nicotine replacement products, the hazard ratio for self-harm among people prescribed varenicline was 1.12 (95% CI: 0.67–1.88), and it was 1.17 (0.59–2.32) for people prescribed bupropion. There was no evidence that varenicline was associated with an increased risk of depression ($n = 2244$) (hazard ratio: 0.88 (0.77–1.00)) or suicidal thoughts ($n = 37$) (1.43 (0.53–3.85)).

In the monitoring study by Kasliwali et al.⁴⁶, the most frequently reported psychiatric events during treatment included (n ; % of cohort) sleep disorder (43; 1.6%), anxiety (33; 1.2%), depression (29; 1.1%), abnormal dreams (26; 1.0%), and mood change (17; 0.6%). Two cases of attempted suicide were reported during treatment with varenicline; however, the authors reported that these patients had previous



history of psychiatric illness and precipitating factors for the event. Another monitoring study by Harrison-Woolrych and Ashton⁴⁷ in New Zealand evaluated the occurrence rates of psychiatric adverse reactions in a general population prescribed varenicline between April 2007 and March 2008. The study included 3,415 patients. They found that sleep disorders were the most frequently reported psychiatric events with an *N* of 56 (4.3%) patients in the responder population. Symptoms of depression were reported by 39 (2.98%) patients (24 new-onset depression, 14 worsening of pre-existing depression, and 1 report of impaired motivation). Serious psychiatric reactions including suicide (one case), suicidal ideation (two cases), and psychotic reactions (three cases) were also identified. Six self-harm events (one fatal, five non-fatal) were identified in the total cohort, giving an occurrence rate of 0.18% (95% CI: 0.06, 0.38) in this population.

The US FDA sponsored two large retrospective cohort studies to explore possible relationships between varenicline and neuropsychiatric events. One study, conducted by the Department of Veterans' Affairs, compared varenicline to NRT and found no statistically significant difference in the risk of negative neuropsychiatric events at one month after being prescribed varenicline or NRT. This study did not specifically quantify suicidality or suicide rates. The second study was conducted by the Department of Defense and found no excess of psychiatric hospitalizations at 30 or 60 days for patients being prescribed varenicline or NRT. It is possible that these studies did not capture all serious adverse events that did not lead to hospitalization. However, their value lies in the number of patients examined as well as the real-world setting that does not exclude medical or psychiatric comorbidities²⁹

Meta-analyses of randomized controlled trials to date have not supported a correlation between neuropsychiatric adverse events and use of varenicline. Gibbons and Mann⁴⁸ reanalyzed data from the 17 placebo-controlled RCTs (*N* = 8,027) of varenicline conducted by Pfizer to assess possible neuropsychiatric adverse events. They found that varenicline increased the risk of nausea (OR 3.69, 95% CI 3.03–4.48) but not the rates of suicidal events, depression, or changes in behavior. A history of current or past psychiatric illness increased the risk of neuropsychiatric events equally in patients treated with varenicline and those receiving placebo. They also used a large Department of Defense (DOD) observational study (*N* = 35,800) to compare acute rates of neuropsychiatric adverse events in patients receiving varenicline or NRT. After propensity score matching, the overall rate of neuropsychiatric adverse events was significantly lower for varenicline than for NRT. In a 2013 Cochrane review examining 14 varenicline trials, no difference was found in terms of serious adverse events (neuropsychiatric or cardiac events) when comparing varenicline and placebo.²⁹ Finally, in a recent review, Hughes⁴⁹ examined post-marketing analyses, case reports, clinical trials, uncontrolled observational studies, controlled observational studies, and studies in smokers with psychiatric problems that have

tested this association. Two pooled analyses of 10 and 17 placebo-controlled trials failed to find more suicidal outcomes in the varenicline condition. Seven large uncontrolled observational studies reported low rates of suicide outcomes in varenicline users (<0.1%), and one study reported a higher rate (6%). Five large controlled observational studies did not find more suicide outcomes in varenicline users than in those using prescribed bupropion or over-the-counter nicotine medications. Small placebo-controlled trials and observational studies of smokers with current psychiatric problems did not find that varenicline was associated with suicidal outcomes.

Overall, it would appear that among the more valid study designs (pooled analyses of placebo controlled trials or large controlled observational studies), there is consistent evidence that varenicline either does not cause increased suicide outcomes, or if it does, the effect is very small.

Summary of pharmacotherapies. The research regarding the use of pharmacotherapies for use in smoking cessation demonstrates often confusing and conflicting results regarding risks of depression, irritability, and suicidality. It appears that nicotine replacement therapies are more effective than placebos, equally effective to each other and to bupropion SR, but not as effective as varenicline. However, the risks of suicidality or other negative moods and behaviors appear to be lowest in NRT. Both bupropion SR and varenicline not only appear to have support for effectively facilitating smoking cessation but also carry low but increased risks for negative affect, behavior, and suicidality. Varenicline appears to have the most research support for increasing risks of suicidality, although the data are mixed and more recent well-controlled studies do not appear to support that varenicline demonstrates increased risk. Additional studies are currently underway under the direction of the FDA. A recent clinical trial, conducted by Pfizer (Study Evaluating The Safety and Efficacy of Varenicline and Bupropion For Smoking Cessation In Subjects with and without a History of Psychiatric Disorders (EAGLES), clinicaltrials.gov identifier NCT01456936), is specifically designed to examine depression and other psychiatric events in varenicline users compared to users of bupropion, nicotine replacement, and placebo in people with and without prior psychiatric problems. Results are expected in 2017. Until that time, it would appear that NRT and bupropion may be the best option for first-line treatment approaches for smoking cessation, but that varenicline should not be discounted or discouraged, but used with full disclosure to the patient.

Psychological Therapies

Psychological treatments such as cognitive behavioral therapy (CBT) and mindfulness-based approaches use strategies that are different from pharmacotherapy to help assist in smoking cessation and may be used alone or in conjunction with pharmacotherapy. CBT is an evidence-based psychological treatment approach that focuses on identifying and challenging maladaptive thoughts, emotions, and behaviors that



may trigger or maintain a variety of difficulties, including depression, anxiety, and smoking. Through changing thoughts and behaviors, this treatment has been demonstrated to help improve mood symptoms and reduce cravings as well as facilitate smoking cessation.^{22,50} Mindfulness-based approaches to smoking cessation focus on helping the smoker develop a different relationship with triggers and cravings through development of skills to increase awareness and presence in the moment without automatically reacting.⁵¹ Mindfulness-based strategies may also positively impact mood.⁵² There are multiple components and techniques involved in both CBT and mindfulness-based psychotherapies, and the research literature is not always clear on their definition of these interventions. Thus, in our review below, we examine studies that identified a CBT or mindfulness-based approach containing at least one of the core components of either CBT or a mindfulness approach, namely a focus on changing behavior, thoughts, or emotions in the case of CBT, or in the case of mindfulness, a focus on helping the patient become more aware of and being in the present moment including their urges/cravings and triggers, and learning how to be present in a nonjudgmental manner, as well as focus on changing their relationship with cravings or urges.

Cognitive behavioral therapies. Cognitive behavioral therapies (CBTs) theorize that mental disorders, including mood and addiction disorders, are maintained by cognitive, emotional, and behavioral factors, although the etiology of such disorders may be multicausal, including genetic components. Thus, in CBT, the treatment is focused on identifying, arresting, challenging, and replacing these maladaptive or erroneous behaviors, emotions, and thoughts with more adaptive and effective ones, thus improving the symptoms or behaviors and ultimately the disorder.^{22,96} Many techniques are used, typically in a structured or manualized format, and often with a case formulation approach to tailor the treatment. There is a focus on behavioral modification techniques including extinction and development of new more adaptive healthy coping behaviors to replace smoking. CBT has a strong research literature demonstrating a positive impact on mood disorders such as depression^{53,54} and has demonstrated effectiveness in treating addiction in general,⁵⁵ smoking specifically,^{50,56,57} and in smokers with co-morbid depression and other addictions.⁵⁸

There are multiple components to a CBT approach to smoking cessation, and it typically contains preparation, quitting, and maintenance or relapse prevention phases of treatment. Initial mechanisms may include aspects of motivational interviewing to help promote readiness to change behavior. If motivational interviewing techniques are not employed in a patient who is not ready or motivated to change, CBT strategies are hypothesized to be of limited value, since therapy typically involves the patient collaborating and working in setting goals and changing behavior and thinking.⁵⁹ Cognitive behavioral therapy focuses on facilitating and maintaining change by using a variety of behavioral and cognitive

strategies. These include reducing cravings and withdrawal symptoms through repeated exposure to situational triggers (cognitive exposure therapy (CET), which gradually reduce symptoms and amount of smoking,⁶⁰ reducing smoking craving through exercise (exercise assisted reduction then stop (EARS)),⁶¹ virtual exposure to negative cigarette behavior (virtual extinction)⁶² manipulating rewarding drug-related memories and reorganizing (extinction and reconsolidation of memory),⁶³ diverting attention from smoking visuals (attentional bias modification),⁶⁴ and reducing negative internal judgments by using cognitive strategies to evaluate and revise self-statements, including thoughts that one cannot cope without a cigarette.⁶⁵ Additional components of a CBT program may include providing information about tobacco, a behavioral contract through which the patients pledge to attend the sessions and quit smoking, self-monitoring and graphical representation of cigarette smoking, strategies for controlling nicotine withdrawal symptoms, physiological feedback (measured by CO and cotinine), training in alternative and/or competing behaviors, social reinforcement of objectives completion and abstinence, and relapse prevention strategies. Such psychotherapies provide addicted individuals various approaches to discontinue smoking, particularly emphasizing effective personal learning styles. Research supports that CBT is effective for a wide range of individuals who are trying to quit smoking, including PTSD patients,⁶³ people living with HIV,⁶⁶ individuals with mental illness,⁶⁷ low socioeconomic smokers,⁵⁷ adults with chronic pain,⁶⁸ overweight and disadvantaged smokers,⁶¹ and youth.⁶⁵ CBT has been demonstrated to be more effective than NRT alone in promoting smoking cessation.⁵⁶ CBT added to Contingency Management, a purely behavioral reinforcement strategy where smokers are rewarded for abstinence with vouchers that can be exchanged for rewards, has been demonstrated to be effective in reducing smoking and was also demonstrated to be more effective than CM alone.⁶⁹ Rates of abstinence in these studies may double the rates of control groups when included. For example, the Sykes and Marks⁵⁷ study describes a randomized-controlled trial of CBT with smokers from an underprivileged area of London. At six-month follow-up, 21 (17.2%) of 122 participants receiving therapy were abstinent and 14 (11.5%) had reduced cigarette consumption by at least 25% of pre-treatment level. Six (5.6%) of 107 participants in the information only control group were abstinent and none had reduced consumption. CBT added to pharmacotherapy has also been demonstrated to improve compliance and reduce potential weight gain associated with smoking cessation⁷⁰ as well as improve mood symptoms when combined with bupropion in psychiatric populations trying to quit smoking.⁷¹ Thus, CBT smoking cessation approaches may be appropriate choices, especially for those interested in drug-free smoking cessation strategies or those who wish to augment pharmacotherapy. CBT does not have the troublesome physical side effects of pharmacotherapy, but it does take motivation and



effort on the part of the patient, as well as access to trained providers, which must be taken into consideration.

The benefits of CBT appear to outweigh risks, and studies of CBT demonstrate improvement in depression, anxiety, and negative affect,^{65,72} which may directly or indirectly decrease suicidality risks associated with smoking cessation.^{67,73,97,98} CBT has shown considerable success in reducing suicidality risk through reduction of hopelessness, suicidal ideation, and suicidal behavior.⁷⁴ In a study examining the impact of CBT with or without an added component to address anxiety, Capron et al.¹⁸ found that suicidality as assessed by the Inventory of Depression and Anxiety Symptoms⁷⁵ was lowered in both groups, but was statistically significantly lower in the group receiving the augmented CBT. Unfortunately, the majority of CBT studies for smoking or nicotine cessation do not specifically describe how many participants report suicidality after instigating therapy or post-treatment unless these data are reported as significant adverse events during the study, and these rarely make it into the manuscript. Thus, we have little information regarding the specific incidence of suicidality in patients who are trying to quit smoking by engaging in CBT only. We do know that the risk of suicide has shown to increase when smoking decreases, even for persons without prior psychopathology. For persons already possessing a history of mental illness, declines in smoking that lead to significantly heightened anxiety, depression, and suicidal ideation are a concern. However, the majority of patients who successfully or unsuccessfully quit smoking using CBTs do not appear to increase their risk of psychopathology and are not at higher risk for suicidality.⁶⁷

Contextual CBTs/mindfulness-based psychotherapies.

Mindfulness-based therapies (sometimes referred to as contextual CBTs) focus on helping patients understand how thoughts, emotions, and body sensations trigger negative habits and cravings, and thus lead to psychological disorders. These treatment approaches hypothesize that by becoming more cognizant or mindful of these potential triggers, patients are better able to avoid negative habits.⁵¹ A key difference between contextual CBTs and traditional CBT is the emphasis on mindfulness and acceptance strategies to reduce the impact of internal triggers on substance use behavior (eg, altering the context and function so cravings, distress, or thoughts of using are less likely to lead to substance use).⁷⁶ These interventions include mindfulness-based smoking cessation and acceptance and commitment therapy.

Mindfulness-based treatment approaches have been the most researched of the contextual CBTs for substance use and other psychiatric disorders. Mindfulness-based therapies have been demonstrated to help patients overcome psychiatric disorders including anxiety and depression.⁷⁷ While further evidence is needed to better understand mindfulness as a component of treatment for substance use, recent reviews of the evidence indicate its efficacy for promoting abstinence and reducing cravings.^{51,78–80,95} Recently, research by Brewer et al.⁷⁸

demonstrated the effectiveness of mindfulness-based therapies by randomizing participants to either mindfulness therapy or an alternative empirically supported cognitive-based therapy called Freedom From Smoking or FFS.⁸¹ These researchers found that 36% of participants receiving mindfulness training achieved abstinence compared to 15% of participants in the alternative treatment group. After a 17-week follow-up, 31% of the mindfulness cohort remained abstinent compared to just 6% of participants receiving the alternative. Brewer et al.⁷⁸ concluded that mindfulness training is an effective method to help people quit smoking. These authors further promote that the 17-week point prevalence odds ratio of 6.75 in their mindfulness-based intervention group was significantly larger than the average odds ratio of behavioral therapies as reported in the current clinical practice guidelines, such as those targeting negative affect (OR = 1.2, abstinence rate = 13.6%), social support (OR = 1.5, abstinence rate = 16.2%), practical counseling (OR = 1.5, abstinence rate = 16.2%), aversive smoking (OR = 1.7, abstinence rate = 17.7%), and medication + counseling (OR = 1.7, abstinence rate = 22.1%).⁸²

Tang et al.⁸³ also found a mindfulness-based therapy to be an effective treatment for smoking cessation. Tang divided participants into two cohorts: (1) integrative body-mind training (IBMT), which is a contextual or mindfulness based psychotherapy focused on implementing meditation or (2) traditional relaxation training. Participants receiving IBMT reduced their smoking habits by 60% by the study's end, whereas there was no demonstrated reduction in the relaxation group. Brain scans revealed that participants in the IBMT cohort also experienced increased activity in the parts of the brain responsible for self-control. Tang et al.⁸³ concluded that mindfulness training increases smokers' self-control and reduces the likelihood that smokers will act on their cravings.

Recently, several randomized controlled trials (RCTs) have suggested Acceptance and Commitment Therapy (ACT) as another promising contextual CBT for substance use.^{76,84} While ACT includes mindfulness as a treatment component, its approach differs from other mindfulness-based treatments in that the concept of mindfulness within ACT is tightly integrated with other processes of change such as acceptance, values, and behavior change methods and ACT protocols often include a less heavy emphasis on meditative practices. ACT uses a combination of acceptance, mindfulness, and values-based therapeutic processes to foster psychological flexibility, which involves learning how to mindfully observe inner experiences such thoughts, feelings, and bodily sensations but not necessarily react to them. There is a focus in ACT on discovering values to guide thoughts and behavior.⁸⁴ As applied to substance use disorders, patients are taught accepting and mindful ways of relating to inner experiences, rather than engaging in substance use (eg, in response to cravings or escape negative affect), while moving forward in building meaningful patterns of activity that are further inconsistent



with substance use. Because of the transdiagnostic nature of ACT, it can effectively target common comorbid psychological disorders such as depression and anxiety.^{85–87} Lee et al.⁷⁶ conducted a meta-analysis that included 10 studies, of which, five were smoking cessation outcome studies and included an N of 918. All studies employed ACT and compared it to other active empirically supported treatments including CBT and NRT or bupropion. Lee et al.⁷⁶ found a small-to-medium significant effect size favoring ACT over other active treatments ($g = 0.42$, 95% CI = 0.19, 64, $z = 3.64$, $P < 0.001$, $k = 5$).

A study by Ruscio et al.⁸⁸ evaluated the impact of a brief mindfulness intervention versus a control condition, upon affect, craving, and smoking behavior and employed ecological momentary assessment to gather real time data. Based on results from 37 participants, for the intervention group, she reports significant reductions in overall negative affect, $F(1, 1798) = 13.8$, $P = 0.0002$; reduced craving immediately post-meditation, (Group \times Assessment Type interaction, $F(2, 1796) = 12.3$, $P = 0.0001$); and reduced cigarettes smoked per day over time (Group \times Day interaction, $F(1, 436) = 5.50$, $P = 0.01$). Suicidality was not assessed directly, but it may be inferred that reductions in negative affect may reduce suicidality risks. Unfortunately, mindfulness based or contextual CBTs for smoking cessation have even less published research on the impact of suicidality than CBT and most studies do not include information about suicidality.

Summary of psychotherapies. Research appears to support significant success rates for smoking cessation and smoking reduction for CBT. CBT appears to be an effective drug-free option to consider for individuals looking to reduce and/or quit smoking and may also successfully be used in conjunction with pharmacotherapy.^{50,56,57} Additionally, although relatively new to the scene and many studies do not specifically address this issue, contextual CBTs such as mindfulness-based therapy and ACT appear to demonstrate success in treating nicotine addiction and promoting smoking cessation with minimal or no reported increased risk of suicidality.^{76,78,88} CBT, mindfulness-based interventions, and ACT have a documented research history of reducing depressive symptoms, and CBT has been demonstrated to help reduce suicidality in smokers trying to quit.¹⁸ There is less known about the benefits of each of these psychotherapies in reducing risk of suicidality in active smokers who are trying to reduce or quit their intake, and many studies implementing psychotherapy in the smoking population do not report data regarding suicidality.

No Treatment

Although numerous clinical trials support medical and behavioral interventions as successful tools for smoking cessation, a significant proportion of the smoking population chooses to opt for an unassisted approach by abruptly stopping their smoking patterns altogether. In fact, almost two-thirds of all people seeking to quit try this *cold turkey* method.⁸⁹ Despite

the large number of individuals who attempt to quit smoking unassisted, research supports that unassisted quitting methods are less effective than medical or psychological therapies. In one population study surveying 10,355 individuals, researchers found that those using medication in combination with behavioral therapies were, on average, three times more likely to stay quit and remain abstinent than those not using any cessation interventions.⁹⁰ In another study, abstinence rates for unassisted quitters were about 7% compared to 15.2% for quitters assisted with counseling methods and various therapies.⁹¹ Researchers Baillie et al.⁹² established a baseline abstinence rate for unassisted individuals of 7.33%, consistent with Kotz et al.⁹⁰ study.

The above findings are significant when considering the connection between smoking cessation and suicidality. Numerous studies have linked nicotine dependence and withdrawal to depression, with nicotine-dependent individuals being more than twice as likely to experience a major depressive disorder than those without a nicotine dependence history.⁵ Because depression is linked to increased risk of suicidality, and because those who quit smoking *cold turkey* will likely have a more difficult time dealing with nicotine withdrawal symptoms than those who are part of a longer-term intervention program, unassisted individuals are possibly at a higher risk for depression and suicidality.¹⁶ These are important factors to consider when planning an optimal intervention for smoking cessation.

Conclusions

In this paper, we briefly reviewed the most frequently utilized treatments for smoking cessation, focusing not only on the ability of the treatment to impact smoking reduction and cessation but also on the connection between the treatment and reduction in risk of suicidality. Current smoking is associated with an increased risk of suicidality.^{2,93} Several treatment options are available to assist individuals wishing to quit smoking, including various pharmacotherapies and psychotherapies. Unfortunately, such treatments rarely come without any side effects or caveats. Pharmacotherapies of any kind typically have side effects other than the intended effect and smoking cessation medications are no different. There have been mixed results regarding the increased risk of suicidality with the use of certain pharmacotherapies for smoking cessation. Some medications for smoking cessation may also be expensive and thus not available for patients. Therapy is not without limitations, including possible negative effects such as the potential for revealing additional psychological trauma or issues that may worsen other symptoms when the patient is trying to focus on smoking cessation. Additionally, psychotherapy requires that patients seek and comply with treatment and that they are motivated to engage and work to change behavior. Trained practitioners have also traditionally provided psychotherapy and patients may not always be able to find a qualified practitioner who is affordable and available



to provide treatment. Thus, the question of which smoking reduction or cessation treatment approach may be effective in promoting smoking cessation while causing the least risk is challenging to determine. Internet and online treatments are growing in popularity but knowledge of their impact or efficacy in helping reduce smoking or promote cessation is less well studied at this time. The connections between smoking cessation treatments and increased risk of suicidality are complex and sometimes contradictory, as has been reviewed in the present article. Both bupropion and varenicline appear to have support for effectively facilitating smoking cessation, but early research supported an increased risk for negative affect, behavior, and suicidality. Varenicline appears to have the most research support for increasing risks of suicidality although the data is mixed and more recent well-controlled studies do not appear to support that varenicline demonstrates increased risk. In more recent studies, these medications appear to demonstrate no increased risk of suicidality. Reasons for these mixed findings may include having more well-controlled studies currently, as opposed to the past. The fact that recent studies appear to exclude patients with serious depression or history of suicidality, who would presumably be at greater risk for suicidality during the treatment trial and/or when quitting smoking, may also play into the recent findings of less increased risk of suicidality with these medications in more recent research. Psychotherapies such as CBT do not appear to have a significant risk of increasing suicidality and appear to work at least moderately effectively to help reduce or quit smoking. In early research findings, the newer psychotherapies such as contextual mindfulness based CBTs also appear to demonstrate at least moderate effect on smoking cessation. Although these mindfulness based treatments also appear to have a positive impact on mood symptoms such as depression, there is currently little research regarding their impact on reducing suicidality in individuals trying to quit smoking. Given that pharmacotherapy has been shown to be the most effective intervention for increasing the odds of success in smoking cessation, but may increase the risk of suicidality, even modestly,^{20,28} it may be that the combination of cognitive and/or behavior therapy plus pharmacotherapy could have a synergistic effect of improving quit success rates, while also providing protection from any increased risk of suicidality.⁹⁰

Further development and refinement of treatments to help promote smoking cessation are necessary and vitally important if we are to positively impact the overall health of millions of people addicted to nicotine. Smoking cessation can be aided by employing effective pharmacotherapies and psychotherapies, but the risks of such treatments must be examined and balanced against the benefits. Future research should continue to explore and document possible correlations and causal relationships between various therapies for smoking cessation and increased risk of suicidality as well as positive impact. It may be useful to further evaluate which

patients demonstrate increased risk for suicidality during clinical trials. For instance, in some research reports, when the circumstances of the suicidal behavior were investigated, it was discovered that the patient was responding to traumatic events or had a history of severe depression prior to going on the medications. Many of the psychotherapy studies have not documented suicidality and this should be addressed in future studies. Exploration of the impact of combination treatment should also include replication studies of clinical trails as well as studies of the impact of psychotherapy on reducing depressive symptoms during smoking cessation, preferably including well-powered randomized trails with long-term follow-up and processes of change analysis.

Author Contributions

Conceived and designed the research review: JKP, JMP, MRH, SN, JA, AOO, JCF. Wrote the first draft of the manuscript: JKP, JMP, MRH, SN, JA, AOO, JCF. Contributed to the writing of the manuscript: JKP, JMP, MRH, SN, JA, AOO, JCF, CPM, JAS, JEF, JNH, ZS. Agreed with manuscript results and conclusions: JKP, JMP, MRH, SN, JA, AOO, JCF, CPM, JAS, JEF, JNH, ZS. Jointly developed the structure and arguments for the paper: JKP, JMP, MRH, SN, JA, AOO, JCF. Made critical revisions and approved the final version: JKP, JMP, MRH, SN, JA, AOO, JCF, CPM, JAS, JEF, JNH, ZS. All the authors reviewed and approved the final manuscript.

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