The American Journal on Addictions, 1–14, 2021

ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/ajad.13171

Nicotine Inhalation and Suicide: Clinical Correlates and Behavioral Mechanisms

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Background and Objectives: Extensive evidence links smoking and suicide independently of psychiatric diagnoses, but there are questions about the pathophysiology and specificity of this relationship. We examined characteristics of this linkage to identify potential transdiagnostic mechanisms in suicide and its prevention.
Methods: We reviewed literature that associated suicide with smoking and e-cigarettes, including the temporal sequence of smoking and suicide risk and their shared behavioral risk factors of sensitization and impulsivity.
Results: Smoking is associated with increased suicide across psychiatric diagnoses and in the general population, proportionately to the number of cigarettes smoked per day. Rapid nicotine uptake into the brain through inhalation of conventional cigarettes, electronic cigarettes (e-cigarette), or even second-hand smoke can facilitate long-term sensitization and short-term impulsivity. Both impair action regulation and predispose to negative affect, continued smoking, and suicidal behavior. Intermittent hypoxia, induced by cigarettes or e-cigarettes, synergistically promotes impulsivity and sensitization, exacerbating suicidality. Two other shared behavioral risks also develop negative urgency (combined impulsivity and negative affect) and cross-sensitization to stressors or to other addictive stimuli. Finally, early smoking onset, promoted by e-cigarettes in never-smokers, increases subsequent suicide risk.
Conclusion and Scientific Significance: Prevention or cessation of nicotine inhalation can strategically prevent suicidality and other potentially lethal behavior regardless of psychiatric diagnoses. Medications for reducing smoking and suicidality, especially in younger smokers, should consider the neurobehavioral mechanisms for acute impulsivity and longer-term sensitization, potentially modulated more effectively through glutamate antagonism rather than nicotine substitution. (Am J Addict 2021;00:00–00)

Received October 14, 2020; revised February 26, 2021; accepted March 6, 2021.
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INTRODUCTION

Rationale

Suicide is the leading cause of injury-related death in the United States, exceeding motor vehicle accidents and homicide, and is increasing.[1] Death by self-injury now exceeds death from diabetes mellitus, but with a younger age distribution.[2] Suicide risk crosses psychiatric diagnoses,[3,4] as does its relationship to smoking.[5] Smoking is the leading cause of preventable medical morbidity and mortality worldwide.[6] We will discuss mechanisms by which smoking may contribute, directly or indirectly, to behaviorally induced mortality through suicide. Suicide risk occurs in a much broader segment of the population than only those with psychiatric diagnoses who have also shown this association with suicide.[7] Transdiagnostic associations of smoking with suicide may extend beyond those with psychiatric disorders like depression. This suggests behavioral mechanisms underlying suicidality, which may not be directly causal, offer targets for alternative approaches to suicide prevention, including pharmacotherapies and behavioral treatments targeting smoking and nicotine use as a contributing risk factor.

We will review the epidemiology of smoking and its reported risk for suicide or severe injurious behavior, identifying potential neurobehavioral mechanisms underlying this association. Contemporary neurobiology, with its wealth of mechanistic data, has challenged the nine traditional Bradford Hill criteria for discovering mechanisms in epidemiological associations, but several are relevant to this review, including the strength of association, consistency, specificity, temporality, biological gradient, plausibility, and experimental data.[8] We will assess potential nicotine-related mechanisms through (a) correlates of exposure to biologically effective doses of nicotine, (b) plausible biological contributors to behavioral mechanisms, such as the speed of nicotine entry into the brain and partial

hypoxia, (c) altered behavioral functions as shown in experimental studies of nicotine effects, and (d) early biologic effects in adolescent nicotine users.

Objectives

Using Bradford Hill criteria, we focus on five potential aspects of relationships between smoking and suicide:

(1) What is the strength and consistency, across study populations and designs, of evidence associating smoking with suicide and related high-risk behaviors?
(2) What biological relationships occur between rapid nicotine availability through inhalation, whether from cigarettes, second-hand smoke, or electronic nicotine delivery systems (ENDS), and behavioral effects of nicotine, potentially abetted by transient hypoxia?
(3) How specific is this suicide-nicotine association, and how does nicotine inhalation interact with other risk factors that have similar behavioral mechanisms?
(4) What are the roles of stress, negative affect, and impulsivity on nicotine use and on immediate regulation of suicidal behavior?
(5) What are the long-term effects of adolescent nicotine exposure on behavioral sensitization or cross-sensitization to stressors or addictions?

The resulting potential cycle of increasing nicotine use and susceptibility to stress-related negative affect and impulsivity is a potential psychopharmacological target for the prevention of suicide through smoking cessation agents that are not nicotine-based substitutions.

METHODS

This review combines data from different disciplines and methods using PRISMA group principles and the Bradford Hill criteria for discovering causation based on epidemiological associations, adjusted for the cross-disciplinary focus and heterogeneous designs of the relevant studies.[8,9] Many studies and reviews have focused on smoking and suicide epidemiology, but few have addressed potential mechanisms for this relationship.

Characterization of Apparent Associations

Specific examples will use the Bradford Hill criteria of *strength of association* since several large epidemiological studies report smoking as a highly significant predictor of suicide.[10] The *consistency of the association* is demonstrated across populations and study designs, focusing here on results generated using cohort and case-control designs (see Table 1). We will address the *plausible behavioral mechanisms criterion* by focusing on impulsivity, among the three major contributors to suicidality in the traditionally high-risk smoking group of psychiatric patients.[5] *Biological plausibility* is strong for the underlying neurobiology of rapid nicotine delivery to the brain through cigarettes or electronic cigarettes (e-cigarettes)/ENDS, potentiating the impulsivity that accompanies suicidal behavior.[30] Concerning *specificity criteria*, high nicotine concentrations without any of the other typical components of cigarettes clearly attract youth to ENDS as their preferred initiation to smoking, supporting the specificity of suicide for nicotine rather than other components of cigarettes and smoking-related medical disorders.[31-33]

Information Sources and Search

We sought peer-reviewed articles related to (a) the epidemiology of smoking and suicidal ideation or behavior, as listed in Table 1, and (b) neurobehavioral mechanisms, particularly sensitization and impulsivity, as contributors to nicotine effects on smoking and suicide. Although we had no language restrictions, essentially, all articles were in English. Study designs ranged from epidemiological or descriptive studies to experimental studies of smoking and/or suicide and their behavioral mechanisms. Reference searches of PubMed, since 1970, included "smoking," "nicotine," "suicide," "electronic cigarettes," and "electronic nicotine delivery systems," with complementary searches combining these terms with "impulsive behavior," "response inhibition," "negative urgency," and "behavioral sensitization." Studies of smoking and suicide mortality, summarized in Table 1, included only primary reports of data from nonoverlapping data sets. We excluded studies from overlapping groups of subjects and those not reporting odds ratios (OR) or relative risks (RR) for smoking and suicide. We also included neurobehavioral mechanism-related topics as needed for our discussion.

Limitations in Methods and Synthesis of Results

The epidemiological studies varied in comparison groups and measures of risk, preventing quantitation of converging endpoints. Many studies (even prospective) relied on quantitative recall of smoking details, except for one study based on the current diagnosis of tobacco use disorder rather than self-reported estimates of smoking.[13]

RESULTS: EPIDEMIOLOGY AND PHARMACOLOGY

We will review the epidemiology of nicotine and suicide followed by the relevant nicotine pharmacology, which supports the potentially synergistic characteristics of long- and short-term action regulation linking smoking and suicidal behavior. We will then review the epidemiology of smoking's association with suicide, and with high-risk behaviors that frequently precede suicide, in some detail. Turning to the pharmacology of nicotine, we will and examine how mechanisms of nicotine delivery to the brain can impact immediate and long-term neurobehavioral processes of impulsivity and sensitization, which potentially underlie relationships between smoking and action regulation that could lead to suicidal behavior. We also address potential behavioral effects on impulsivity and sensitization,

TABLE 1. Smoking and suicide fatalities

References	Design	*N*	OR, smoking	Dose/CPD	Controlled for
Angst and Clayton[11]	Prospective birth cohort	2782	**7.9** (2.9-26.6)	82% of suicides smoked daily by age 18	1, 2, 4
Balbuena and Tempier[12]	Case-control (mortality follow-back)	989 suicides 3125 hom. or accident; all >100 cigs.	Duration: **2.3** (1.3-3.9); quit: **0.4** (0.3-0.6)	Suicide: Increased duration of smoking	1, 2, 4
Bohnert et al[13]	Prospective Cohort (3 years)	4,863,086	**1.88** (1.76-2.02)	Tobacco use disorder	1, 2, 4, 5
Chen et al[14]	Prospective (12 years)	162,682	**3.69** (1.85-7.39)	<versus> 20 CPD, direct or SHS	1, 2, 5
Evins et al[15]	Prospective, twin	16,282	**3.5** (2.3-5.2) **2.3** (1.6-3.2)	>20 CPD, $P = .017$	1, 2, 3, 5
Hemenway et al[16]	Cohort (12); women	121,700	**1.9** (1.2-3.1)L **4.2** (2.7-6.6)H	L < 24, H > 24 CPD	NA
Hemmingsson and Kriegel[17]	Prospective cohort	49,323	**3.0** (1.7-5.3) (unadjusted)	Positive ($P < .02$)	1, 2, 3, 4, 5; adjusted NS
Iwasaki et al[18]	Retrospective cohort	45,209	**2.1** (1.1-4.0)	>60 pack-year ($P < .036$)	1, 5
Jee et al[19]	Prospective cohort	1,234,927	**1.7** (1.3-2.2) **2.8** (1-4.7)	M < F	5
Korhonen et al[20]	Prospective, twin pairs; 14-22 years old	1330	**4.45** (2.4-9.7)	Daily smoking	1, 2, 4
Lucas et al[21]	Prospective cohort	253,033	**2.7** (2.1-3.4)	$P < .001$ vs CPD	1, 2, 3, 4, 5
Miller et al[22]	Prospective (9 years)	300,000	**2.3** (1.2-4.6) >20 CPD	$P < .001$ vs CPD	1, 2, 3
Miller et al[23]	Prospective (8 years)	51,529	2.5 (0.9-7.3) **4.3** (2.2-8.5)	< vs >15 CPD	1, 2, 3, 5
Riala et al[24]	Prospective (20 years)	10,934	**4.05** (1.18-13.93)	Reg. daily > light, $\chi^2 = 15.8$	1, 4
Schneider et al[25]	Case-control	552 (163 cases)	M: **2.6** (1.3-5.2)	Excluded cluster B	4
Schneider et al[26]	Cohort (12 years)	12,888	**2.23** (multivariate)	NA	1, 3, 4
Smith et al[27]	Cohort (12 years)	361,662	**1.9** (1.3-2.3) "implausible"	CPD $\chi^2 = 76$; $P < .0001$	1, 3, 5
Sonderman et al[28]	Cohort; "external" causes of death	73,422	**1.7** (1.4-2.2)	Suicide > Accident, homicide	1, 2, 3, 4, 5
Tanskanen et al[29]	Prospective, 14.4 years	36,527	Smoke, alcohol, caffeine: **4** (1.8-8.8)	"Linear" vs CPD	

Bolded values have statistical signiciance, $P < .05$.
Controlled for 1 = demographics; 2 = alcohol and/or SUD; 3 = health habits; 4 = psychiatric disorder (affective or psychotic); 5 = medical illness.
CPD = cigarettes per day; F = female; M = male; OR = odds ratio; SHS = second-hand smoke; SRB = suicide-related behavior.

exacerbated by intermittent hypoxia associated with smoking. These two behavioral mechanisms in younger smokers may identify those at risk and suggest preventive pharmacological treatments for suicide that target these mechanisms rather than use nicotine substitution. In the "Discussion" section, we will elaborate on these two neurobehavioral mechanisms that could underlie this apparent association of smoking and suicide.

Epidemiology of Smoking and Suicidal Behavior

Smoking and Suicide Mortality

Table 1 summarizes evidence on smoking and risk for suicide based on retrospective and prospective cohort, case-control, and twin designs. In addition to the consistently demonstrated increase in suicide risk across study designs, in almost all cases, the increase was proportional to the number of cigarettes smoked per day (CPD), controlling for varying potential confounders.

This table raises several key points. First, retrospective studies of large national samples with over 4000 deaths show ORs of 2.1 to 2.3 for suicide and smoking and of 0.3 for years of abstinence and suicide.[12,18,34,35] Second, prospective cohort studies also reported increased suicide rates in smokers. The RR for suicide was 2.3 (95% confidence interval [CI] 1.2-4.6) in 300,000 male soldiers who smoked more than 20 CPD.[22] Three large cohorts found a multivariate RR of 2.7 (95% CI = 2.1-3.4) for smokers vs nonsmokers, with RR rising to 4.1 (95% CI = 3.0-5.8) for those smoking ≥25 CPD.[21] A similar large male cohort found an RR of 4.3 (95% CI = 2.2-8.5) for suicide in heavier smokers.[23] During a 14.4-year follow-up of 36,527 individuals, suicide risk was markedly increased and proportionate with CPD compared to nonsmokers.[29] In an 11,000-member birth cohort followed for 20 years, adolescent daily smokers had an increased risk for suicides.[24] Third, exposure to second-hand smoke increased suicide.[14] Finally, a prospective cohort study of 16,282 twin pairs found a hazard ratio for smoking and suicide of 3.5 (95% CI = 2.3-5.2) for over 20 CPD and 2.3 (95% CI = 1.6-3.2) for fewer CPD, while twin pairs doubly discordant for smoking and suicide showed an OR of 6.0 for suicide in the smoking twin,[15] underscoring the potential role of genetics.

The studies in Table 1 cover about 36 years. Over that time, the rate of smoking decreased by at least 50% in the general population of the United States, but did not decline in people with severe psychiatric or substance-use disorders.[36,37] People with psychiatric disorders are more likely to smoke,[38] and are less likely to quit,[39] than other smokers. If the relationship between suicide and smoking were a general population association, it would not necessarily change with the decline in smoking in the general population, while if it was disease-specific, it might be expected to increase. In fact, it appears superficially to have weakened nonsignificantly (RR vs year of publication $r = -.227$, $df = 16$, $P > .3$), consistent with lack of specific relationship to psychiatric diagnosis. However, it is difficult to interpret relationships between the time of publication and the smoking-suicide RR across studies because of variation in (a) the nature of the populations studied, (b) how smoking behavior was operationalized, (c) study design, and (d) study durations.

Controversy on Smoking and Suicide. There is consistent evidence for a relationship between smoking and suicide across study designs, but there have been questions about its specificity. Smith et al[27] reported, in 361,662 subjects, that smoking was associated with increased suicide, controlling for medical illnesses or other potentially smoking-related problems. The authors concluded that a smoking-suicide relationship was "physiologically implausible" and likely to result from an unidentified artifact. However, a subsequent study reported a physiological association between nicotine use and reduced serotonergic function, potentially related to suicidal behavior.[40] Hemmingsson et al[17] reported that in a population with a high rate of severe alcohol problems, correction for alcohol-use disorder eliminated the significant unadjusted OR for smoking and suicide. Leistekow[41] rebutted Hemmingsson's conclusion, stating that the study population was atypical and that the statistical analyses covaried away a clinically significant finding. Similarly, a significant association between smoking and suicidal behavior in individuals with psychotic disorders was eliminated by the addition of covariates, including recent self-harm.[42] In other studies, the effect of smoking was significant despite the effects of alcohol or other drugs.[11-15,20,22,23,28] "Risky alcohol use" and smoking had independent effects on suicide[43] and suicidal behavior[44] in patients with depression.[43,44]

The complexity of temporal relationships among smoking, other risk factors, and suicide suggest that common mechanisms interact across risk factors for suicide.[45] Smoking can both predispose to and result from behaviors like impulsivity combined with negative affect (negative urgency, see below), which are involved in suicide.[46-48] Characterizing effects of nicotine could clarify transdiagnostic mechanisms in suicidal behavior and possibly lead to physiologically strategic interventions.

A Mendelian randomization study of smoking and suicide attempts or ideation suggested possible "genetic confounding" by characteristics of impulsivity or behavior control.[49] This was an intriguing result that demonstrated the multidirectional and probably nonlinear relationships among complex behaviors. It should be kept in mind that (a) the study subjects had suicidal ideation or plans but not attempts, so were a more heterogeneous group with less severely focused risk than those with fatal (Table 1) or potentially lethal[50-54] attempts. Mendelian randomization is a promising and potentially elegant strategy but is dependent on genetic markers with suitable specificity across smoking, suicide, and action control, which are not characteristic of most available GWAS results.[55]

Meta-Analyses. Recent meta-analyses address relationships between smoking and suicide across large populations. A meta-analysis of the 15 studies from 1966 to 2011, involving 2395 suicides among 1,369,807 participants, found a pooled RR for suicide compared with never-smokers of 1.8 (95% CI = 1.5-2.2) for current smokers, with suicide risk increasing by 24% for each 10 CPD.[56] A subsequent analysis of 63 studies involving 8,063,634 subjects verified that current smoking was associated with a progressively higher risk for suicidal ideation, plan, attempt, and death.[7]

Smoking and High-Risk Behaviors Associated With Suicide

Smoking is associated with increased deaths from injury in general. Crude RR for death from injury in smokers was 1.9 (95% CI = 1.3-2.7). The RR was 2.1 (95% CI = 1.1-4.1) for motor vehicle accidents, potentially related to impaired action control.[35]

While suicide attempts greatly outnumber deaths, medically severe suicide attempts predict subsequent suicide and other premature mortality: all-cause mortality increased 15-fold in men and 9-fold in women over 5 years after medically severe suicide attempts.[50] Risk was highest during the first year[51] and persisted for over 10 years.[51] Posthospital survival time correlated negatively with trait-impulsivity.[53] Since 60% of premature deaths after medically severe suicide attempts were not from suicide,[53] medically severe attempters have high general premature mortality risk. Over half of suicide fatalities are first attempts,[54] so identifying risk factors like smoking, poor behavior control, and severe suicidal ideation is essential to formulate preventive action before suicide attempts occur.

The National Epidemiological Study of Alcohol-Related Conditions (NESARC; 2004-2005; $n = 34{,}653$) found that lifetime and past-year nicotine dependence were associated with suicide attempts, adjusting for psychiatric disorders and physical disease.[52] Former smokers had fewer suicide attempts than current smokers, controlling for prior suicidality and psychiatric diagnoses.[57] A prospective study of adolescents and young adults reported that suicide attempts were associated with occasional cigarette use (OR = 1.8 [95% CI = 1.2-2.7]). In a 12-month prospective study of National Guard members, smoking increased suicide ideation (OR = 2 [95% CI = 1.3-3.2]).[58]

Smoking and depression have a bidirectional relationship[59]: Smoking, both conventional cigarettes and ENDS, is the leading cause of avoidable illness and death in depression, and depression predisposes to smoking (discussed below). Over the 2 years after major depressive episodes, the three strongest predictors of suicidal acts were additively history of attempt, severity of depression, and cigarette smoking.[60] In a cohort of 5445 college students, elevated depressive symptoms predicted e-cigarette use within 6 months.[61] In the same cohort, increased frequency of tobacco product use and contemporaneous use of multiple tobacco products were associated with higher depressive symptoms.[62] Current cigarette smoking also predicted current and 9-month suicidal ideation and behavior and was a leading predictor of repeated suicide attempts in bipolar disorder.[63,64]

Summary

Extensive evidence links cigarette smoking to suicide and to other high-risk behaviors. Suicide risk appears proportional to current smoking, regardless of psychiatric diagnosis. The relationship between smoking and suicidal behavior also is proportionate to the severity and specificity of suicidality, with the relationship of suicide death > attempt > plan > ideation. However, to date, there is little evidence on the specificity of this relationship. Such information is vital given its potential relationship to transdiagnostic mechanisms in suicide and its prevention.

Nicotine Delivery to the Brain and Suicide Risk

As with any reinforcing stimulus, rapid delivery of nicotine to the brain is more reinforcing and more likely to precipitate impulsive behaviors and sensitization than slow, steady delivery, such as with nicotine patch replacement therapy.[32] The extensive pulmonary absorption area delivers nicotine to the arterial circulatory system, bypassing peripheral venous circulation and first-pass hepatic metabolism to reach half-maximal brain concentrations within 15 to 30 seconds[65] and maximal concentrations in 2 to 4 minutes.[66] Systemic absorption, such as from gum, patches, or even intravenous infusion, is slower.[66] Nicotine concentrations decline rapidly after each puff, leading to a "rush" followed by pressure to continue smoking.[65,66]

ENDS (e-Cigarettes)

Cigarettes are not the only rapid nicotine delivery system. ENDS deliver nicotine to the brain as rapidly as conventional cigarettes and may be similarly associated with suicidality.[67] ENDS consist of a device to aerosolize and inhale nicotine with kinetics resembling conventional cigarettes,[32,33] leading to similar potentials for abuse and addiction. ENDS are less strictly regulated than combustible cigarettes; associated risks increase as they become more popular.[32,33] These products' risks are exacerbated by inconsistent estimates of nicotine concentration, which can be higher than in cigarettes,[31,68] potentially toxic flavoring and aerosol compounds,[68] and unreliable labeling with poor regulation.[69] ENDS exposures and poisonings, especially in young children, are increasing[70,71] with reports of toxicity and death in children and adults,[71,72] including suicide.[73,74] Accidental ingestion is more common under, and suicidal ingestion over, 10 years of age.[75]

ENDS and Smoking: Cessation vs Initiation. ENDS could reduce smoking-related suicidal behavior by promoting smoking cessation, but evidence for their effectiveness in smoking cessation is weak. In fact, there is robust evidence for the role ENDS play in the uptake of cigarettes.[31,33] Youth and young adults whose first introduction to nicotine is via

ENDS subsequently report using a wide range of combustible products that deliver nicotine, and even when people quit or reduce conventional cigarette use, they may continue to use ENDS, maintaining efficient delivery of nicotine to the brain.[31,69,76-78] Reports of recent national data show adolescents using ENDS more commonly than conventional cigarettes.[79]

Database searches have found only low-quality evidence for ENDS efficacy in smoking cessation; a recent prospective cohort study found no differences in smoking cessation between ENDS users and nonusers.[78] A Cochrane review found evidence supporting ENDS for smoking cessation to be of low to very-low quality[78]; another meta-analysis found that ENDS possibly *reduced* smoking cessation.[79] A more recent study found that nicotine-containing ENDS were modestly effective in increasing 6-month smoking abstinence in adults.[80] In other studies, participants continued to use ENDS instead of quitting nicotine use.[31,76,77] A more recent Cochrane Review was more favorable in terms of cigarette cessation (6% improvement vs comparators),[80] but the association between ENDS use and reduced nicotine exposure remains modest at best (6% improvement vs comparators, with 4% vs comparators using non-nicotine ENDS). The Cochrane Reviews focused on randomized trials for smoking cessation in adults, while a major concern of this current review is the potential role of ENDS in the initiation of smoking, particularly in adolescents.

The potential role of ENDS is especially crucial for increasing both suicide risk and conventional cigarette smoking in youth. ENDS are increasingly popular among adolescents and other never-smokers.[75,79,81-83] Use of ENDS predicted conventional cigarette initiation in a four-wave (every 6 months) study of 2558 cigarette-naïve college students. Among those reporting cigarette initiation by wave 4, previous ENDS users significantly outnumbered nonusers. Wave 1 ENDS use predicted subsequent cigarette initiation additively with other risk factors. A prospective cohort study in 1506 never-smoking young adults aged 18 to 30 found that cigarette smoking was initiated by 47.7% of ENDS users and 10.2% of nonusers ($P = .0001$). ENDS use at baseline was independently associated with smoking initiation at 18 months (adjusted OR [AOR] = 6.8 [95% CI = 1.7-28.3]).[81] A 2-year longitudinal study of 3474 adolescents confirmed that nicotine-containing ENDS use was associated with escalating ENDS use and initiation of conventional cigarettes.[82] In a three-wave longitudinal study of adolescents, ENDS use was associated with future cigarette use across all three waves, without association between cigarette and future ENDS use.[82] Prevention of ENDS use among youth may prevent future use of cigarettes.[30,84,85]

ENDS and Suicidality. ENDS may be associated with depression and suicidality in adolescents because ENDS (a) deliver nicotine rapidly to the brain[67]; (b) can lead to conventional cigarette smoking[81,82]; (c) can cause cerebral hypoxia (see below); and (d) are widely used in young never-smokers because of advertising, flavorings, and lack of regulation.[85] There is little direct information on ENDS and suicide, but the Korean Youth Risk Behavior Web-based Survey ($n = 62,276$) found that dual users and ENDS-only users (lifetime and current) had higher rates of depression and suicidality than did nonusers.[86] A subsequent report in 5405 middle- and high-school students found that ENDS use had progressively increasing OR for suicidal ideation, plan, attempt, and serious attempt (OR = 3.09 [95% CI = 1.51-6.62]).[87]

Second-Hand Smoke

Second-hand smoke exposure was associated with increased suicide attempts and related suicidal ideation in women who had never smoked,[88] suggesting that deliberate nicotine-seeking is not necessary for its behavioral effects. The possibility of severe behavioral consequences of inhaled nicotine in people who have never smoked also has substantial consequences for adolescents living with parents who smoke in the house.

Smoking or second-hand smoke exposure[89] during adolescence is associated with increased suicidal behavior 10 to 20 years later.[14,15,24] While a quantitative relationship varies and is difficult to estimate,[89] inhalations of more than 20 CPD via passive or active nicotine exposure similarly increased subsequent suicide risk.[14] Increased risk requires 20 CPD in the household, so exposed nonsmokers living with several "light" smokers potentially experience similar suicide risk to those actively smoking 20 CPD.[14] Prevention of early nicotine inhalation can reduce later adult daily smoking and early-onset suicidal behavior,[20,82,83,85] but this may require reduction of nicotine use throughout the household or workplace.

An extreme example of early exposure to second-hand smoke is prenatal exposure to maternal smoking, associated with earlier experimentation with smoking, smoking progression, and nicotine dependence.[90] Earlier experimentation occurred more often in prenatally exposed boys, and increased dependence, in girls. Prenatal nicotine exposure could induce nicotine sensitization and/or reflect heritable maternal impulse-control problems.

Suicidal Behavior, Hypoxia, and Smoking

Suicide is linearly related to living at a high altitude (OR increase 1.2/1000 m of altitude).[91,92] Exposure to hypoxia, from altitude, smoking, or ENDS, was associated with increased suicides in 9,620,944 people with 22,403 suicides.[91] ENDS have a similar or greater risk relative to conventional cigarettes, causing high levels of intermittent hypoxic stress even without nicotine.[93] Intermittent hypoxia may interact with nicotine in susceptibility to nicotine dependence, possibly through impaired serotonin synthesis,[93] working synergistically with direct effects of nicotine on serotonergic function.[36] Children with obstructive sleep apnea are susceptible to impulsive behavior[94]; young adults with impulsivity and polysubstance abuse have reduced cerebral

oxygenation.[95] Thus, smoking-related intermittent hypoxia could increase behavioral susceptibility to short- and long-term adverse effects of nicotine or other drugs.

DISCUSSION

How are Smoking and Suicide Related?

Figure 1 summarizes interactions between risk for suicide and current nicotine inhalation, including ENDS and second-hand smoke. We have reviewed extensive evidence linking nicotine inhalation and suicide risk, but basic questions remain regarding mechanisms and specificity of this association.[30] Potential relationships linking suicide and smoking include: (a) smoking-related diseases; (b) direct effects of nicotine; and (c) a correlative relationship where increased suicidal behavior in smokers appears coincidental because of shared risk factors.[30] Such a relationship may appear spurious, but if smoking introduces, shares, or exacerbates the risk factor, it is clinically and mechanistically significant. Truly independent bivariate, unidirectional relationships may be rare and elusive in complex behaviors. We will discuss the time course of smoking and suicide risk, followed by common risk factors shared by smoking and suicide. The following sections will elaborate immediate- and long-term behavioral mechanisms by which smoking may predispose to suicidal behavior.

Time Course of Smoking and Suicide Risk

Consequences of Early Smoking Onset

Over 80% of adult daily smokers started smoking before age 18.[6] Adolescence is crucial in mutual exacerbation of smoking and behavioral disorders.[97-99] Fifty percent of severe adult psychiatric illness has started by 14 years of age, and 75% by 24 years.[100] In 1330 twins (aged 14-22 years), early-onset regular tobacco use was associated with increased risk for intentional self-injury at age 22 (AOR = 4.6 [95% CI = 1.9-10.8]).[20] In adolescents, daily cigarette smoking is associated with current suicidal ideation; CPD had linear relationships to future intentional self-injury (AOR = 4.5 [95% CI = 2.0-9.7]) and suicidal behavior (AOR = 2.1 [95% CI = 1.1-4.1]), controlling for depression and alcohol or other substance-use disorders,[101] underscoring the potential importance of preventing early smoking.

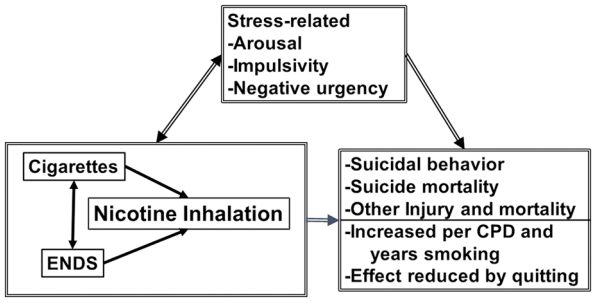

FIGURE 1. Smoking and behavioral risk. Inhaled nicotine increases suicidality (Table 1) and fatal injuries.[35] Stress-related arousal, impulsivity, and negative urgency increase, and are increased by, nicotine inhalation, mediating its effects on suicide,[32] a self-perpetuating increase in nicotine use.[96] Either ENDS or combustible cigarettes can precede the other, but a major concern is the increasing role of ENDS in early-onset nicotine use.[79,81-84] CPD = cigarettes per day; ENDS = electronic nicotine delivery systems.

ENDS may accelerate the smoking onset and amplify relationships between early behavior disturbance and smoking.[83,84] Sensation-seeking predisposes to ENDS use, in turn, increasing adolescent and early adulthood cigarette experimentation.[102,103] Mendelian randomization found similar genetic propensities for initiation of cigarettes or of ENDS, which are possibly related to impulsivity.[104] Further, adolescents and young adults find ENDS are especially attractive agents for starting nicotine inhalation and continued ENDS use may accelerate and strengthen impulsivity. Prevention of ENDS initiation and this strengthening of impulsivity may prevent nicotine-associated impaired action regulation.

Smoking-related behavioral problems may precede suicidal behavior. In a birth-cohort study ($n = 2782$), 50% of suicides did not have a history of a major psychiatric disorder; most of those with psychiatric diagnoses did not have a major depressive disorder.[11] Eighty-two percent of suicides were smokers, compared to 40% of the overall group; this high rate of smoking may explain the lack of a significant relationship between suicide and alcohol use disorder in that study. A prolonged and/or escalating pattern of poor behavioral control was described with premature death in students on probation; suicide was the most common cause of violent death.[104] This pattern has been consistently linked to smoking.[28,35]

Temporal Relationship Between Nicotine Inhalation and Suicidal Behavior

Suicide risk is higher in current than in former smokers,[12,14,21,57,58] and correlates with current CPD.[18,21-23,29,51] Suicide risk also increases dose-dependently with second-hand smoke exposure.[88,89] Among twins discordant for smoking and suicide, the smoking twin had a higher suicide risk (OR = 6), again suggesting a pharmacological, proportionate relationship to nicotine exposure.[15]

Risk Factors Common to Smoking and Suicide

Medical Illnesses

Cigarette smoking often accompanies the pulmonary or cardiovascular disease, alcohol misuse, affective disorders, schizophrenia, and posttraumatic stress disorder (PTSD), all of which are associated with suicide. These conditions, however, do not generally account for the suicide risk associated with smoking.[13,15,17,23,54]

Shared Risk Factors in Alcohol and Smoking

The National Survey on Drug Use and Health reported that alcohol and illicit drug use are more common among

current cigarette smokers (67%) than among nonsmokers (48%). Similarly, binge drinking (43% vs 17%) and heavy drinking (15% vs 4%) are more common among smokers. Early onset of smoking and alcohol use are strongly associated.[98] Alcohol-dependence or smoking increases the likelihood of the other about fourfold.[99] Alcohol or other substance-use disorders[10,15,22,23,35,100] or psychiatric disorders[15,54,58,101] do not generally account for reported associations between smoking and suicide. Exceptions[17] may be related in part to characteristics of study populations.[37] The relationship between alcohol use and suicide may not require a diagnosable alcohol-use disorder; increased acute alcohol-use and associated impulsivity may be part of a process of impaired immediate behavior control predisposing to suicidal behavior.[102,105-107] Some of these factors could be synergistic with smoking[30] or, as discussed below, share underlying mechanisms.

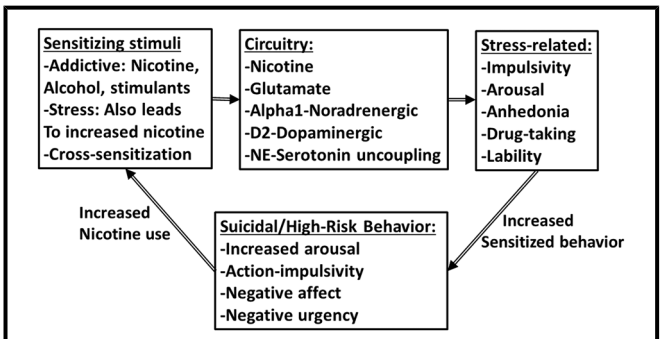

FIGURE 2. Nicotine and sensitization to addictive or stressful stimuli. Nicotine is a sensitizing stimulus.[32,109] In addition, nicotinic receptor stimulation is required for sensitization regardless of the sensitizing stimulus,[110] predisposing to stress-related impulsivity and arousal,[111] increasing nicotine use, especially with negative affect[108] and predisposing to suicidal behavior.[111,112] NE = noradrenergic.

Summary

Smoking is associated with medical and psychiatric illnesses, but these associations do not account for its apparent relationship to suicide. Instead, younger age of smoking initiation appears more important for increased risk for later suicide. Two potential contributors to this association with age of onset are: (a) the greater likelihood of smoking persistence for early-onset than later-onset smoking, and/or (b) greater susceptibility to immediate and long-term behavioral effects of nicotine in pre-adolescence and adolescence than in adulthood. These two onset age possibilities merit further investigation.

Potential Neurobiological Mechanisms Underlying Smoking, Suicide Risk, and Behavior: Impulsivity and Behavioral Control

Mechanisms of Impulsivity and Behavioral Risk in Smoking

Impulsivity and Risk-Taking. Sensation-seeking typically appears during adolescence, along with alcohol and cigarette experimentation. In 1132 Mexican-American youth aged 11 to 13 years, the onset of smoking over 3 years was associated with social and behavioral disinhibition. Age, linguistic acculturation, drug or alcohol use, and thrill- or adventure-seeking were associated with increased social disinhibition in a multivariable model ($P < .001$).[97] Social disinhibition leads to sensation-seeking, predisposing to ENDS use in youth, which, in turn, leads to cigarette use in adolescents[102] and young adults.[103] In a longitudinal cohort study ($n = 947$, age 15-21 years), impulsivity was higher in smokers than in nonsmokers, correlated with CPD, and was stable across time.[108] Impulsivity increases the risk of becoming and remaining a smoker.

Smoking induces negative urgency, the tendency to respond to negative affect with impulsivity (Fig. 2). Smokers high in anxiety-sensitivity had increased negative urgency,[47] which links impulsivity to cigarette smoking[46] as well as to smoking initiation or relapse.[47] Negative urgency was associated with longer puffs and shorter intervals between puffs, consistent with rapid and poorly modulated uptake of nicotine.[96]

Role of Nicotine in Suicide-Related Neurobehavioral Mechanisms

We will address relationships between nicotine and apparently contrasting aspects of behavioral control. Impulsivity drives an immediate lack of behavioral regulation, and long-term lack of behavioral regulation results from behavioral sensitization to rewarding or traumatic stimuli. Impulsivity and sensitization are strongly related in their contributions to lack of behavioral regulation, and nicotine contributes to both impulsivity and sensitization.[111] First, we will discuss nicotine's contribution to impulsivity and then to sensitization.

Mechanisms of Impulsivity. Three conceptualizations of impulsivity are involved in addiction and in suicide risk: (a) Trait-impulsivity (susceptibility to impulsive behavior and cognition), (b) rapid-response or action-impulsivity (inability to conform action to its context), and (c) reward-delay or choice-impulsivity (inability to choose a larger delayed reward over a smaller immediate reward or increased delay discounting).[108,111] Heavy drinking and daily smoking have additive effects on impulsivity[113] as well as suicidal behavior.[43] Drug-induced changes in impulsivity and associated behavioral sensitization may be critical in the transition to and maintenance of nicotine dependence. Adolescents not achieving abstinence have increased action- and choice-impulsivity.[108] Figure 2 shows the effects of impulsivity as impaired action regulation on onset and maintenance of smoking. Impulsivity with

negative affect or negative urgency also potentially mediates the effects of smoking on suicidal behavior.

Impulsivity Results From an Imbalance Between Facilitation and Inhibition of Action. Action-impulsivity, increased across recurrent or trauma- and addiction-related disorders,[111] predisposes to suicide.[112] Noradrenergic (NE) hyperfunction is associated with impulsivity and its associated autonomic and subjective activation in humans.[111,114] Stressful or addictive stimuli, via α1-NE receptors, impair inhibitory functions of the prefrontal cortex,[115] increasing impulsivity[114] and disrupting the activation-inhibition balance that can protect against suicide. Choice impulsivity, the inability to delay response for a larger reward, is also related to smoking, producing hopelessness and lack of future-sense even without a depressed mood.[116] Anti-serotonergic effects of nicotine may further promote impulsivity in people making suicide attempts.[40]

High-Risk Behavior Combines Activation and Depression. Impulsivity, hopelessness, and suicidal behavior are associated more strongly with depression and activation combined than with either alone.[117] This combination, related to negative urgency,[46-48] can occur outside of conventionally defined psychiatric illnesses. Impulsivity can predispose to hopelessness and dissociate hopelessness from depressed mood.[46,116] Impulsivity during depression can predispose to suicidality,[112,118] exacerbated by the relationship between trait-impulsivity and hyper-arousal.[119] Trait-impulsivity is higher in persons with both a suicide plan and an attempt than with a suicide attempt or plan alone[120]; "impulsive" individuals are more likely to act on a "planned" attempt. Impulsivity with depressive symptoms produces negative urgency, linking smoking to suicide risk.[121]

Role of Cumulative and Immediate Stress. Stress is associated with increased nicotine craving and impulsive responses in smokers, who experience greater stress-induced risk-taking, including suicidal risk behaviors than do nonsmokers. Cumulative stress is further associated with an increased risk of smoking.[122] Impulsivity also mediates the relationship between stress and cigarette use in adolescent smokers,[123] and adolescent smoking cessation can decrease stress-related risk-taking.[124] Cumulative stressors in the context of nicotine-facilitated sensitization could exacerbate suicide risk.[31]

Summary

Impulsivity, or impaired immediate action regulation, predisposes to smoking and to suicidal behavior. In turn, smoking can increase impulsivity. Stress or stress-sensitivity strengthens the relationship between smoking and impulsive behavior, and the combination of impulsivity and negative affect, called negative urgency, particularly strengthens this relationship to suicide.

In Susceptible Individuals, Highly Stressful or Rewarding Stimuli Produce Behavioral Sensitization, Predisposing to Addictive and Suicidal Behavior

Figure 2 shows that severe or repeated exposure to highly salient (reinforcing-addictive or aversive-traumatic) stimuli[106,120] can elicit development of sensitization and cross-sensitization in humans,[122] with enhanced behavioral and physiological responses to similar or related stimuli. Rapid stimulus onset facilitates sensitization.[32] Sensitization requires a complex interaction of neurotransmitter systems, including type 2 dopamine receptor and α1-noradrenergic receptor stimulation,[123] with uncoupling of noradrenergic-serotonergic transmission,[124] and nicotinic[125,126] and glutamate[127] receptor stimulation. Therefore, nicotine is not only itself a sensitizing stimulus,[31,126] but is integral for sensitization to other addictive or stressful stimuli.[125] Accordingly, the OR for PTSD and smoking is about 4 (95% CI = 2.1-7.7).[93] Trait-impulsivity increases susceptibility to sensitization,[127] and is elevated in individuals at risk to develop trauma- or substance-related, affective, and psychotic disorders.[106] Expression of sensitized behavior, in turn, increases action-impulsivity,[128] with stress-induced anhedonia and hyper-arousal.[106] By predisposing to stress-induced impulsivity, negative arousal, and anhedonia, behavioral sensitization, from early trauma or substance-use, increases suicide risk.[105] Nicotine directly and indirectly increases behavioral sensitization[109,125,126]; smoking facilitates this by delivering nicotine rapidly to the brain.[129] This can lead to a self-perpetuating cycle of nicotine inhalation and sensitized, potentially high-risk, behavior.

Treatment: Potential Role of Sensitization Blockade

We have outlined a possible framework for high-risk behaviors leading to suicide and its facilitation by nicotine, based on the combination of activation and depression and their relationship to sensitized behavior. Suicidal behavior and nicotine use (cigarettes and ENDS) are increasing among adolescents and young adults. Therefore, innovative approaches to early smoking prevention or cessation seem a powerful way to reduce suicides and other dangerous correlates of suicidal behavior. As discussed above, ENDS may have only limited value in reducing suicide associated with tobacco smoking and may increase the risk for further combustible nicotine use.[69,73,76,77] Neurobiology of smoking and suicide can offer viable alternatives to current treatments, such as patches, ENDS, or varenicline, which rely on nicotine substitution.

Sensitization and action regulation may be targets for smoking cessation and protection against its behavioral effects, including suicide. *N*-methyl-D-aspartate (NMDA) antagonists can prevent sensitized behavior.[119,130] Reducing sensitized behavior[111] with the NMDA receptor antagonist

ketamine reduces suicidal ideation,[131] independent of depression or anxiety.[132] NMDA or metabotropic glutamate receptor blockade also facilitates smoking cessation.[133,134] Ketamine-like drugs have the potential for abuse or sensitization at higher doses,[135] but other NMDA modulators, which are potentially effective in humans, may not.[130] Glutamate modulation is a promising component of effective smoking cessation[134] and of early antisuicide intervention in high-risk populations who may have already experienced sensitizing addictive or trauma-related stimuli.

Summary

Sensitization to traumatic or addictive stimuli can increase stress-related impulsive behavior and negative urgency. Nicotine is a sensitizing stimulus and is required for sensitization to other stimuli. A blockade of sensitization expression could break this link between smoking and suicide.

OVERALL SUMMARY AND CONCLUSIONS

We applied Bradford Hill criteria to the epidemiology, nicotine pharmacology, developmental factors, psychopathology, and effects on immediate and long-term behavior regulation as supports for building a causative model for the association between suicide and smoking, particularly the nicotine component of smoking and ENDS. In summary, our five questions offered several provocative conclusions.

(1) What is the strength and consistency of evidence associating smoking with suicide and related high-risk behaviors? We found that, across study designs, smoking is dose-dependently associated with suicide, as well as attempted suicide and other potentially lethal behavior.
(2) What biological relationships occur between rapid nicotine availability through inhalation, whether from cigarettes, second-hand smoke, or ENDS, and behavioral effects of nicotine, potentially abetted by transient hypoxia? We suggest that other forms of nicotine inhalation, including passive inhalation and ENDS, appear to have similar risks, possibly exacerbated by intermittent hypoxia. ENDS is becoming strongly associated with the early initiation of long-term nicotine use.
(3) How specific is this suicide-nicotine association? Based on the pharmacological effects of nicotine, smoking may both facilitate and be increased by sensitization to addictive or stressful stimuli.
(4) How does nicotine inhalation interact with other risk factors for suicide that have similar behavioral mechanisms, such as stress, negative affect, and impulsivity? We suggest that disrupted behavior control, related to stress, impulsivity, and negative urgency, can increase the neurobehavioral risk for smoking. In turn, smoking can increase impulsivity, especially negative urgency. More broadly, a recent Cochrane Review found that smoking cessation improves overall mental health.[136] Therefore, clinicians should ask individuals with suicidal ideation or other behavioral risks about smoking history[137] since smoking cessation can be a vital part of treatment that may also reduce susceptibility to other risk factors for suicide.
(5) What are the long-term effects of adolescent nicotine exposure on behavioral sensitization or cross-sensitization to stressors or addictions? We suggest that the greatest behavioral risks of nicotine inhalation, including suicide or other premature death, occur in early-onset users because early-onset nicotine use promotes the development of behavioral disturbances and prolonged regular smoking. ENDS potentially facilitate this early onset. Finally, this early-onset smoking needs early treatment and the pharmacotherapy most suited for this treatment may be glutamatergic antagonism and modulation rather than nicotine substitution.

We thank the Mental Health Care Line, Michael E. DeBakey Veterans Affairs Medical Center, Houston, for support.

Author Contributions

ACS, DPG, AVW, and TRK all contributed to the conception and design of the study and to data acquisition, analysis, and interpretation, participated in writing and revising the article, and reviewed and approved the final version of the submitted manuscript. ACS, the corresponding author, initiated the first draft, coordinated writing and revision of the article, and submitted it after all had agreed to its final form. We have not published or presented this work elsewhere.

Declaration of Interest

ACS has grant support from the American Foundation for Suicide Prevention, the VAMC Cooperative Studies Program, the National Institutes of Health, the Department of Defense, and the Linda and John Griffin Family Professorship in Psychiatry, all without a direct relationship to this paper. DPG and AVW have nothing to disclose. TRK is a consultant for Alkermes, US World Meds, Opiant, BioXcel, Astellas, Otsuka, and Novartis, and receives grant support from the Department of Defense, the Waggoner Endowed Professorship, the Toomim Family Foundation, and the O'Quinn Foundation, which are all unrelated to this paper. The authors, alone, are responsible for the content and writing of this paper. The content and results have not been submitted and/or published elsewhere.

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