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## **Smoking and Suicide: A Brief Overview**

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## Abstract

This article provides a brief overview of the rationales, possible mechanisms and epidemiological data on the association of smoking, smoking cessation and cessation medications with suicide. Current smoking is reliably associated with suicide both in case-control and cohort studies. The three most plausible (but relatively untested) explanations for the association are that smokers have pre-existing conditions that increase their risk for suicide, smoking causes painful and debilitating conditions that might lead to suicide, and smoking decreases serotonin and monoamine oxidase levels. Stopping smoking appears to lead to major depression in some smokers; thus, it could induce suicide; however, smoking cessation has not been associated with suicide in the few studies available. Regulatory agencies have stated bupropion, rimonabant and varenicline appear to be associated with suicide; however, the data for these statements have not been presented in sufficient detail to assess their validity. Most prior data have come from post-hoc analyses. Studies that a priori focus on understanding smoking and suicide are now needed.

#### Keywords

depression; nicotine; smoking; smoking cessation; suicide

## 1. Introduction

Many prior studies have found an association of current smoking and suicide (Leistikow & Shipley 1999). In addition, a recent review cited some evidence that smoking cessation could precipitate a clinical depression (Hughes 2006) and, thus, might lead to increased suicide. Thirdly, a recently published study (Nissen et al. 2008) and data analyses from regulatory agencies (US Food and Drug Administration 2008; US Food and Drug Administration 2007b) suggested bupropion, rimonabant and varenicline--medications marketed for or developed for smoking cessation--are associated with suicide (US Food and Drug Administration 2007b; US Food and Drug Administration 2007b).

The aim of the current review is to provide, in one place, an overview about the association of suicide with 1) current smoking, 2) smoking cessation and 3) use of smoking cessation medications. Prior articles have specifically looked at each of these three associations (Leistikow & Shipley 1999; Breslau et al. 2005; Kessler et al. 2007; Licinio & Wong 2005); however, none has described how these three interrelate, nor possible biological and psychological mechanisms for these associations. The benefits of having such information in

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The term "suicide' can refer to several outcomes; i.e., thoughts, behaviors, attempts or completed suicides. Although each of these may have different determinants, in the literature reviewed herein, the author found no consistent differences across these outcomes; e.g., smoking, cessation or medications were not consistently more strongly associated with one vs. the others; thus, the article will use the simpler term "suicide" to refer to any or all of the above outcomes. Also, terms such as "self-injury" or "self harm" can refer to behaviors in which the intent was not to die; thus, these outcomes have not been included.

## 2. Methods

To obtain information the author initially searched <u>PubMed</u> for the occurrence of the following keywords or stems: "smok\*," "tobacco," "cig\*," "nicotin,\*" "varenicline," "rimonabant," or "bupropion" crossed with "suicid\*" in the title or abstract of articles. A similar search in <u>PsychInfo</u> was performed. Based on reading the titles and abstracts of these citations, the author selected papers to read. In addition, the author conducted searches on <u>PubMed</u> and <u>PsychInfo</u> for reviews on suicide, on the association of suicide and use of antidepressants, and on the safety of cessation medications. References in these papers added other papers. The author queried pharmaceutical companies and regulatory agencies; however, no non-public information was obtained from these companies. Altogether, the author read approximately 180 abstracts and 120 papers. The choice of which papers to include was based on the author's judgment.

## 3. Results

#### 3.1. An Overview of Theories and Mechanisms for Associations of Suicide vs. Smoking, Smoking Cessation or Use of Smoking Cessation Medications

Before reviewing the data on the association of smoking, cessation, and cessation medications with suicide, the article reviews possible reasons to believe such associations might exist. Proposed theories and mechanisms to explain such associations can be confusing because some theories completely contradict each other, and because theories differ in whether they are referring to the association of suicide with a) initiation of smoking, b) current smoking, c) cessation of smoking or d) medication to treat smoking. For brevity, this review will cover the later three associations but will not cover the association of suicide with initiation of smoking.

These theories/mechanisms can be conceptualized as a  $3 \times 3$  matrix with one factor representing whether one believes a) smoking is not causally related to suicide; i.e., smoking is a marker not a cause, b) smoking causes suicide; i.e., smoking is a psychological or physical toxin, or c) smokers have a pre-existing increased risk for suicide and smoke to reduce this risk; i.e. smoking as self-medication. The other factor is whether one is referring to a) risk during current smoking, b) risk during abstinence or c) risk with use of a medication for cessation (Table 1).

#### 3.2 Association of Suicide with Current Smoking

#### 3.2.1. Possible Mechanisms

**3.2.1.1. Smoking as a Non-Causal Marker:** Many studies have consistently found an association of current smoking and risk of suicidal thoughts or behaviors (see Section 3.2.2. below). Current smoking could be associated with suicide due to "third factors" or

"confounders" that are correlated both with smoking and suicide (Hemmingsson & Kriebel 2003; Kessler et al. 2007; Smith et al. 1999). This is plausible because many of the risk factors for suicide (Sudak 1999) are also risk factors for being a smoker; e.g., younger age, non-White, lower income, less education, unmarried, unemployed, less religious, anxiety, depression, psychoses, substance use problems, low self-esteem, risk taking, having a serious physical illness, impulsivity, aggression, antisocial personality, fatalism, emotional instability, etc. (US Department of Health and Human Services 1994). In addition, certain genes appear to predispose to both smoking and depression (Kendler et al. 1993).

One method to test this "smoking as a marker" explanation is to determine if the association of current smoking and suicide is eliminated when such "confounders" are entered as covariates in an analysis (Smith & Phillips 1992). Some of the epidemiological studies described below found the association persisted in spite of entering confounders (Iwasaki et al. 2005; Miller et al. 2000a; Miller et al. 2000b; Tverdal et al. 1993); however, these analyses may be inaccurate because they did not include the most important confounders. Other studies found the association did not persist when "confounders" were entered (Hemmingsson & Kriebel 2003; Kessler et al. 2007; Leistikow et al. 2000; Boden et al. 2007); however, these may be inaccurate because what they classified as confounders are actually probably mediators (Breslau et al. 2005). For example, if the association of smoking and suicide disappears when depression is added as a "confounder" (Breslau et al. 2005), this may not rule out a causal effect of smoking but rather may indicate there is a causal effect of smoking, but it is mediated by increased risk for depression. Thus, future studies should examine "third factors" both as moderators (i.e., confounds) and mediators (i.e., mechanisms) using recent statistical methods (MacKinnon et al. 2007). In summary, whether the smoking as a marker explanation is correct will require a study that includes measures of all the major risk factors for suicide and distinguishes between confounders and mediators. This is likely to occur only in a study that a priori focuses on the association of smoking and suicide.

**3.2.1.2.** Smoking as a Psychological or Physical Toxin: Smoking could cause suicides via several mechanisms. The first posits that smoking worsens mood, impulsivity, aggression and other behavioral factors that predispose to suicide (Parrott 2003). Typically, it is the nicotine in cigarettes that is thought to cause these behavioral problems (Parrott 2003). Several indirect lines of evidence support this explanation. For example, in cross-sectional studies, smokers report more negative affect than never-smokers or exsmokers (Parrott 2003). Similarly, long-term former smokers report less depression than current smokers or when they themselves used to smoke (US Department of Health and Human Services 1990b). Also, when nicotine is given intravenously in higher doses to never-smokers, this results in increased negative affect (Newhouse et al. 1988).

There are plausible mechanisms to account for such behavioral toxicity. Reductions in serotonin have been repeatedly linked to increased hostility, aggression, and importantly, to increased suicide (Kamali et al. 2001). Chronic nicotine exposure reliably reduces serotonin and its metabolites in animals (Olausson et al. 2002). Several studies have examined whether this also occurs in humans. In a postmortem study, smokers had lower levels of serotonin and its metabolites in various brain regions than did nonsmokers (Benwell et al. 1990). Smokers had lower levels of serotonin metabolites in the cerebrospinal fluid (Malone et al. 2003) but not in platelets (Pivac et al. 2004; Schmidt et al. 1997). Smokers also had lower levels of prolactin in response to a serotonin inhibitor (Berggren et al. 2003; Malone et al. 2003; Anthenelli & Maxwell 2000) – an indicator of lower serotonergic function; however, smoking could have influenced prolactin levels by nonserotonergic mechanisms (Anthenelli & Maxwell 2000). Unfortunately, except for the postmortem studies, the above studies were performed only in smokers vs nonsmokers with current alcohol dependence. Also, in these studies, it was unclear whether the control groups of "nonsmokers" were composed of never-smokers only

or never-smokers + ex-smokers. Making this distinction is important to determine whether smoker/nonsmoker differences are due to the direct effects of smoking vs some pre-existing phenomena (Hughes 1996). One line of evidence against this mechanism is that depression and suicide have not been common adverse events from acute or chronic dosing of nicotine per se in humans; i.e., in studies of nicotine replacement therapy (NRT) (Greenland et al. 1998). Of course, this may be because the level of nicotine and the rapidity of absorption of nicotine in NRT does not adequately mimic that of nicotine via cigarettes.

Another possible mechanism is that low levels of monoamine oxidases (MAOs) A and B-enzymes that metabolize noradrenaline--are often, but not always, associated with suicide (Van Kempen et al. 1992). Current smokers have lower levels of MAOs than never-smokers (Fowler et al. 2003; Lewitzka et al. 2008). Importantly, former smokers do not have lower levels suggesting active smoking is what is causing the low MAO levels (Fowler et al. 2003). Also importantly, nicotine itself is not the cause of the lower MAO levels (Fowler et al. 2003); rather harmon alkaloids appear to be the cause (Herraiz & Chaparro 2005).

A third mechanism posits that smoking causes physical illnesses and physical illness is a leading cause of suicide (Sudak 1999). In fact, smoking is probably the leading behavioral cause of ongoing morbidity (Centers for Disease Control and Prevention 2003; US Department of Health and Human Services 2004) and the illnesses smoking causes; i.e., chronic obstructive pulmonary disease, cancer and cardiovascular disease (US Department of Health and Human Services 2004) can cause prolonged pain and disability (US Department of Health and Human Services 2004); thus, it is plausible smoking could cause suicides via causing serious illnesses.

The fourth mechanism is that (a) the nicotine in smoking acts as an antidepressant, and (b) some lines of evidence indicate antidepressants can cause suicide. Nicotine, in low doses, appears to have anti-depressant effects. It reverses learned helplessness in animals (Semba et al. 1998), normalizes sleep patterns in never-smoking depressed patients (Haro & Drucker-Colin 2004), and can act as a partial antidepressant in depressed, never-smoking humans (McClernon et al. 2006). Other studies show a nicotine antagonist can act as an antidepressant (George et al. 2008). Although debatable, some lines of evidence suggest antidepressants increase suicide risk in adults (Mann et al. 2006; Licinio & Wong 2005; Reith & Edmonds 2007). The mechanisms by which antidepressants might increase suicide are unclear; e.g., antidepressants might induce akathesia, aggression, panic attacks, mania, or obsessions (Teicher et al. 1993). One mechanism that might be relevant is that antidepressants might cause chronic insomnia that would worsen mood. Smoking does appear to worsen sleep and, this does appear to be due to nicotine (Haro & Drucker-Colin 2004; Htoo et al. 2004). In addition, several studies have shown that chronic sleep problems can worsen mood (Colrain et al. 2004). Although nicotine given during withdrawal can improve insomnia (Colrain et al. 2004), insomnia is more prevalent with nicotine agonists (Silagy et al. 2004; Greenland et al. 1998; Society for Research on Nicotine and Tobacco 2007) and partial agonists (Cahill et al. 2007; Nides et al. 2006; Keating & Siddiqui 2006; Fagerstrom & Hughes 2007) than placebo in clinical trials. How often insomnia causes significant problems is unclear; e.g., there are no reports of how often smokers stop medications due to insomnia. The other possible mechanism relevant to nicotine medications is that antidepressants "energize" patients so they can act on suicidal ideation (Teicher et al. 1993). Nicotine is clearly a stimulant; however, its stimulant actions differ from those of prototypic stimulants such as the amphetamines (Clarke 1990), are mild, and typically decline as tolerance occurs (Clarke 1990). Finally, it is unclear whether any antidepressant effect of nicotine is via the same biological and psychological mechanisms as traditional antidepressants; thus, it is difficult to know if the concern about antidepressants and increased suicide should apply to nicotine in cigarettes.

**3.2.1.3. Smoking as Self-Medication:** Smoking has been associated with many psychological symptoms and psychiatric disorders (Hughes 1999; Kalman et al. 2005). One explanation of this association has been that those destined to become smokers have pre-existing or "latent" psychiatric or psychological problems and use nicotine to "self-medicate" to abate these (Markou & Kenny 2002). Several epidemiological and biological lines of evidence support this hypothesis (Markou & Kenny 2002). The above section outlined data on how nicotine could improve mood. Nicotine also reliably improves performance in non-humans (Heishman 1998) and, in preliminary studies improves Alzheimer's (Newhouse et al. 2004) and attention-deficit disorders (Levin et al. 2001) in never-smokers. Nicotine also may alleviate cognitive defects in schizophrenia (Dalack et al. 1998). The self-medication explanation would at first appear to predict smokers should have less suicide since they are treating their depression, schizophrenia, etc with smoking. However, typically this explanation posits that nicotine is an inadequate medication, and thus, suicide is still greater in those who smoke.

**3.2.2. Epidemiological/Clinical Data**—Many studies have found cross-sectional and prospective associations of suicide with current smoking; few have failed to find this association. The best studies using nationally-representative samples, as well as prospective designs with long-term follow-ups, have almost uniformly found the two associated (Breslau et al. 2005; Doll et al. 1994; Iwasaki et al. 2005; Leistikow et al. 2000; Miller et al. 2000b; Miller et al. 2000a; Tverdal et al. 1993). The association was present whether suicidal thoughts, plans or completions were used as the dependent variable. The odds ratios and relative risks typically were greater than 2.0. In several studies, the risk persisted even after major depression, alcohol/drug abuse, other psychiatric disorders, or other confounders were controlled for.

#### 3.3. Association of Suicide and Smoking Cessation

**3.3.1. Possible Theories and Mechanisms**—The above section dealt only with the association of suicide and current smoking. Whether longer term cessation would be expected to be associated with increased suicide differs across the three explanations in Table 1. The "marker" explanation would predict any association would remain but would still be due to confounds. The psychological/physical toxin theory would predict that since cessation would stop the toxic effects of smoking, there should be no association of suicide with former smoking. The exception would be if one hypotheses that some of the toxic effects of smoking are irreversible; e.g., if smoking caused a painful and debilitating disease that continues after smoking cessation. Finally, the self-medication theory would predict that suicide behavior should increase with abstinence as smoking is no longer present to abate suicidal ideation.

In terms of actual data, many lines of evidence indicate smoking causes a physical dependence on nicotine and this results in a withdrawal syndrome (Hughes 2007a) that includes worsened mood and other behaviors that would increase the risk of suicide (Hughes 2007b). Many studies have found that negative affect symptoms are the most common symptoms of tobacco withdrawal (Hughes 2007b) and several studies suggest smoking cessation can precipitate a clinical depression in a subset of smokers (Hughes 2006). Thus, increased suicidal behavior early on after cessation due to nicotine withdrawal is clearly plausible. In contrast, most data indicate that prolonged abstinence for months or years (i.e. well after withdrawal is abated) is associated with less, not more, depressed mood (US Department of Health and Human Services 1990a).

**3.3.2. Epidemiological/Clinical Data**—Whether smoking cessation increases the risk of suicide during the initial period of tobacco withdrawal symptoms is unclear. In reports of clinical depression post-cessation, (Ayers & Tobias 2001; Hughes 2006) two of the case reports reported suicidal ideation during a post-cessation depressive episode (Bock et al. 1996; Stage et al. 1996). Only one study quantified suicidal ideation early after smoking cessation. In this

study, among the 304 women who tried to stop smoking, 21 (7%) reported suicidal ideation during the 6 mo post-cessation (Tsoh et al. 2000). This study did not have a control group. Although cross-study comparisons are risky, the rate of suicidal ideation in this study is substantially elevated rate compared to the above-cited epidemiological studies of smokers not trying to quit.

A recent meta-analysis provided a more rigorous test of whether cessation might change suicidal behavior (Leistikow & Shipley 1999). This analysis searched for smoking cessation trials in which the rates of smoking cessation were  $\geq 10\%$  greater in the active vs. control condition and had a sufficient sample size to detect suicides. The study located three large randomized controlled trials in which the quit rates were 21–24% greater in the active condition. The pooled rate of suicide in the control conditions in these studies was 15/6786 or 0.22%. In the active conditions (in which much more smoking cessation occurred) it was 10/8740 or 0.11%. This trend for fewer, not more, suicides in the group who had more abstinence was not statistically significant but certainly contradicts the hypothesis that cessation would increase suicidal behaviors.

#### 3.4 Association of Suicide and the Use of Smoking Cessation Medications

**3.4.1. Theories/Mechanisms**—Two of the major medications for smoking cessation are full agonist nicotine replacement therapies (nicotine gum, patch, inhaler, lozenge/microtab and nasal spray) and the partial nicotine agonist varenicline. Since full agonist nicotine replacement therapy (West & Shiffman 2001) and partial agonist therapy (Fagerstrom & Hughes 2007) both reduce nicotine withdrawal including depression, this should reduce the amount of suicide initially after cessation. On the other hand, since these medications are nicotine agents and the same argument stated above -that (a) nicotine is a psychological toxin or (b) since nicotine is an antidepressant, it might cause suicide (see above) -might apply. One could hypothesize that since varenicline is a partial agonist, its antidepressant effects should be less. On the other hand, varenicline does have antagonist effects, and nicotine antagonists appear to have antidepressant actions and thus might have potential to induce suicide (Rabenstein et al. 2006).

There are two proven non-nicotine smoking cessation medications; i.e. antidepressants (McEwen et al. 2006; Hughes et al. 2007) and clonidine (Gourlay et al. 1999). The two proven antidepressants are bupropion--an atypical antidepressant and nortriptyline--a tricyclic antidepressant. The US Food and Drug Administration issued a warning that antidepressants could cause suicide (Gibbons et al. 2005). This warning was based on data from selective serotonin reuptake inhibitors (which are not effective for smoking cessation), but it has been extended to all antidepressants, including bupropion and nortriptyline (US Food and Drug Administration 2007a). On the other hand, given that the biological or psychological mechanism of how antidepressants might increase the risk of suicide is unclear, it is unclear whether to expect the risk to also occur with nortriptyline and bupropion. Although there are no reports about suicide during use of clonidine, an infrequent adverse event from clonidine is depressive symptoms (Prasad & Shotliff 1993) which might lead to suicidal behavior.

Rimonabant, a cannabanoid antagonist, is another non-nicotine medication being developed both as a treatment for obesity and for smoking cessation (Gelfand & Cannon 2006). In two post-mortem studies, completed suicides had higher levels of cannabanoid receptor activation than non-suicides (Vinod & Hungund 2006). In addition, rimonabant acts similar to SSRIs in its effects on neurotransmitters and on animal tests of antidepressant activity; thus, the antidepressant effects of rimonabant could cause it to increase suicidal behavior (Vinod & Hungund 2006).

#### 3.4.2. Epidemiological/Clinical Data

3.4.2.1. Nicotine replacement therapy (NRT): Proven NRTs are nicotine gum, inhaler, lozenge, microtab, nasal spray and patch (Fiore et al. 2008; Silagy et al. 2004). Over 20,000 smokers have been exposed to full nicotine agonists via nicotine replacement therapy in published trials (Silagy et al. 2004). Meta-analyses and reviews of adverse events (AEs) from full nicotine agonists do not report increased suicide nor worsened mood as plausible AEs from nicotine replacement (Silagy et al. 2004; Greenland et al. 1998; Society for Research on Nicotine and Tobacco 2007). The best test of the association of use of nicotine replacement and suicide comes from an analysis from the Lung Health Study, which randomly assigned smokers to nicotine gum or no medication (Leistikow & Shipley 1999; Anthonisen et al. 1994). Over the 5 yrs of the study, the incidence of suicides was not greater in the nicotine gum vs control group. If anything, suicides appeared to be less common with gum; i.e., 2/3923 or 0.05% in the nicotine gum group vs 5/1964 or 0.25% in the control group (Anthonisen et al. 1994; Leistikow & Shipley 1999). The only other data comes from case reports of intentional overdoses of nicotine replacement therapy or bupropion (Montalto et al. 1994; Avers & Tobias 2001; Woolf et al. 1996; Engel & Parmentier 1993; Labelle & Boulay 1999). Interestingly, none of these attempts occurred in the context of using the medication to stop smoking. All appeared to be due to a pre-existing psychological or psychiatric problem.

**3.4.2.2.** Nicotine partial agonists: Among the 2183 smokers exposed to varenicline in published trials, several AEs were more common with varenicline than placebo but suicide and depression were not cited as common AEs (Cahill et al. 2007; Nides et al. 2006; Keating & Siddiqui 2006; Fagerstrom & Hughes 2007). The two studies that reported on post-cessation mood reported varenicline improved mood compared to placebo (Nides et al. 2006; Jorenby et al. 2006). One trial reported a suicide in the placebo group (Oncken et al. 2006). Another trial reported a suicide in the varenicline group in a participant with a past history of depression (Tonstad et al. 2006). A non-RCT found that smokers with a past or current mental disorder did not have greater psychiatric AEs than smokers without this history (Stapleton et al. 2008).

A non-peer reviewed study listed 227 reports of "suicide/self-injury" including 28 cases of completed suicide to the US FDA over a 20 month period (The Institute for Safe medication Practices 2008). The US FDA released warnings for varenicline, citing 491 cases of suicidal ideation, attempts or completed suicides (US Food and Drug Administration 2008) Many of these occurred while using varenicline and continued smoking, suggesting they cannot be attributed to nicotine withdrawal. The US Veterans Association released a similar report citing 32 instances of suicide among 147,718 prescriptions (0.02%) (Department of Veterans Affairs 2008). None of these reports provide more detail and neither concluded causality had been established; however, both believed these data indicate further investigation is needed. Neither report estimated the incidence of suicide in medication users. If one assumes reports of AEs are typically only 1% of the actual rates(The Institute for Safe medication Practices 2008) and that over 5.5 million smokers in the US have used varenicline; then the incidence of all suicidal outcomes is probably less than 1% and the rate of completed suicides is even less.

Cytisine is another partial nicotine agonist that has been tested in 10 trials but only three of these were placebo-controlled (Etter 2006). Among the 8154 smokers exposed to cytisine, no suicidal behavior was reported; however, no psychiatric adverse events at all were reported which suggests under-reporting of this class of AEs in the published studies.

**3.4.3. Antidepressants**—Bupropion has been tested in 40 RCTs and found efficacious (Hughes et al. 2007). The FDA warning about the association of bupropion and suicidality did not provide any data; i.e. the warning occurred simply because bupropion was classified as an

antidepressant (US Food and Drug Administration 2007a). One governmental review reported suicidal ideation occurred in 6 of the 4067 exposed smokers (1:677) to bupropion in the clinical trials conducted for marketing and that this appeared to not be greater than expected (Hughes et al. 2007). A post-marketing report on bupropion from the UK reported 82 suicide-related events over a period in which about 1 million prescriptions occurred for a risk of about 1:100,000 which is a rate of suicides less than that in smokers in general (< 1:10,000) (Hughes et al. 2007); however, post-marketing reports often underestimate events by a factor of 5-20 fold.

Nortriptyline has been tested in eight trials and found efficacious (Hughes et al. 2007; Hughes et al. 2005). Again the FDA warning on nortriptyline was not due to direct data but simply because nortriptyline is an antidepressant (US Food and Drug Administration 2007a). No reports of suicidal behavior or overdoses were reported in the RCTs of nortriptyline for smoking cessation, but combined together, they represent only about 500 smokers exposed to nortriptyline.

Finally, the doses and duration of use of bupropion and nortriptyline when used for smoking cessation are lower than that when they are used for depression; thus, whether any effects found on suicidality among depressed patients would apply to when these medications are used for smoking cessation is unclear.

**3.4.4. Cannabanoid Antagonist**—A trial of rimonabant to decrease obesity and atherosclerosis reported more suicidal outcomes in the active than the placebo group (2.6% vs 1.7%) (Nissen et al. 2008). A US FDA analysis of the nine RCTS of rimonabant for obesity and the four for smoking indicated a higher rate of suicidal behavior with rimonabant than placebo (0.4% vs 0.2%, OR= 1.9) (US Food and Drug Administration 2007b). When the author used the FDA data and recalculated these results just for the four smoking studies using the placebo and high dose group (20 mg, n=3813), the exact same results were found.

### 4. Discussion

#### 4.1. Summary of Results

The above data indicate a) suicide is strongly associated with current smoking; however, whether this is because smoking is a marker for other causes of suicide or because smoking or nicotine actually is a behavioral toxin is unclear, b) suicide might be expected to increase during initial smoking cessation but the little data available does not confirm this, and c) three smoking cessation medications--bupropion, rimonabant and varenicline--have been associated with suicidality in smokers; however, the validity of data for this last association is unclear.

#### 4.2. Limitations of the Review

These conclusions must be tempered by several limitations with the above data. First, suicides and even suicidal ideation are rare events (e.g. the incidence of completed suicide in a lifetime is about 1/10,000 and for suicide ideation is about 1/1000) (Sudak 1999); thus, to detect the onset of suicide in a study lasting only a year probably requires sample sizes of over 10,000. Second, most studies of suicide and smoking have been case-control studies and this type of study almost always suffers from some self-selection or indication bias (Rothman & Greenland 1998; Shiffman et al. 2005; Klungel et al. 2004). None of the case-control studies adequately measured all the important possible confounders. Third, among the few prospective studies; most could have produced false negative reports because those with suicidal ideation may not report it, or may drop out of the study, or may be lost-to-follow-up. Since participants in smoking studies are usually reporting outcomes to non-counselors, they may be especially reluctant to reveal suicidal ideation. In addition, most prospective studies did not mention

suicide; thus, it is unclear if they did not look for an association of smoking and suicide; they looked but did not find it; they found it but did not report it, or they reported it but it was edited out prior to publication.

#### 4.3. Suicide and Current Smoking

Before reading the literature, the author believed any association of current smoking and suicidality would be due to selection bias; i.e., those who chose to smoke are a priori at greater risk to develop psychiatric illnesses, and not due to a causal effect of smoking. However, this selection bias (or smoking as a marker) explanation would posit that ex-smokers should also have increased risk of suicidality; this was not found. Although one could rationalize this by saying smokers who are able to quit are those with no or less psychiatric illnesses, one would still expect to see some increased suicidality in ex-smokers. In addition, the existence of a plausible biological mechanism; i.e., chronic smoking decreases serotonin and MAO and low levels of each are related to suicide makes a causal link possible. Thus, this author believes more direct and generalizable replications of low serotonin and MAO in smokers and their relationship to suicide are needed.

#### 4.4. Suicide and Smoking Cessation

Before this literature review, the author also thought that smoking cessation was likely to lead to increased suicidality by worsening mood initially after stopping smoking, especially among the many smokers with a past history of depression. However, three large studies of abstinence that tracked smokers over long periods found no evidence of this (see section 3.3.2). Although loss to follow-up was not high in these studies, given suicidality is rare, even a study with only 10% drop-out could miss increased suicidality.

#### 4.5. Suicide and Nicotinic Medications for Smoking Cessation

Before this literature review, the author thought smoking cessation medications should be associated with less, not more, suicide given that NRT decreases withdrawal-induced negative affect (West & Shiffman 2001) and appears to have antidepressant effects (Salin-Pascual et al. 1996); However, the post-marketing results cited above do suggest further investigation is needed. Although the incidence of suicide appears small, one could argue that even this is problematic given that medications are not essential to smoking cessation; i.e., many smokers are able to quit without medications (Shiffman et al. 2006). On the other hand, one could argue that there are some smokers who cannot quit without medications (US Dept Health and Human Services 1988), and given the large health benefits from smoking cessation (US Department of Health and Human Services 1990b), a 1% incidence risk is acceptable. At this writing, the US FDA, (US Food and Drug Administration 2008) the European Medicines Agency (EMEA) (European Medicines Agency 2007) and the manufacturers of varenicline (Pfizer 2008) and bupropion (GlaxoSmithKline 2007) have added warnings about suicide. These warnings state smokers considering use of bupropion and varenicline should be screened for a history of psychiatric disorders and monitored closely for psychiatric AEs.

## 5. Future Studies

Given the need for large sample sizes in studies of suicidal ideation/behavior or suicides per se, perhaps the best method to test for an association of suicide and smoking, cessation, or use or medications would be to add questions about suicidal behavior to one of the national surveys on smoking; Even more importantly, questions about suicide should be added to ongoing longitudinal studies of adult smokers. Such studies not only can provide prospective validity tests but also accommodate mediator analysis. One could then examine the prevalence of suicide outcomes in smokers who tried to quit vs. did not, and those who used nicotinic medications vs. did not. Inclusion of data on important confounds (e.g. presence of debilitating

smoking-related illness, psychiatric disorder, withdrawal symptoms and patterns of medication use) would be necessary. However, given the many possible interactions between ongoing smoking, stopping smoking and taking medications, an even better solution would be to include questions about suicide in ongoing prospective cohort studies. As many possible confounds, moderators and mediators as possible should be included. This is important not only to better examine causality but also because the incidence and behavioral mechanisms of suicide likely vary between men and women, older and younger persons, those with vs without existing psychiatric illnesses, etc. It would be of special interest to compare rates of suicide in NRT vs non-NRT medications. Also, a systematic search of all published RCTs of treatments for smoking cessation could compare the incidence of mentions of suicide in the active vs control groups; however, given the brief reporting of AEs in most publications, this could produce a false negative.

Finally, and perhaps most importantly, prospective Phase IV post-marketing studies from pharmaceutical companies or governmental agencies that specifically focus on psychiatric AEs in non-NRT medications should be considered because they have much greater internal and external validity than the current AE reporting system. Inclusion of control groups of smokers trying to quit with NRT or without any medication would be helpful.

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#### Table 1

#### Theories of how smoking, smoking cessation and cessation treatment can influence suicide

	Effect of ongoing smoking on suicide risk	Effect of abstinence on suicide risk	Effect of nicotine medication on suicide risk
Smoking is a non-causal marker Smoking is a psychological/physical toxin	No effect Increases risk	No effect Decreases risk	No effect Increases risk
Smokers are self-medicating suicide risk	Decreases risk	Increases risk	Decreases risk