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Examining antidepressant drug response by smoking status: Why is it important and how often is it done?

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Abstract

Background—Despite an increasingly recognized relationship between depression and smoking, little is known about the degree to which treatment studies for depression consider the impact of smoking on outcomes. The aim of this study is to examine the extent to which smoking is considered in current antidepressant treatment research.

Methods—We conducted a MEDLINE search of recent randomized clinical trials of pharmacotherapy for depression published between January 1 and December 31, 2007, and a search of current pharmacological intervention studies for depression using www.Clinicaltrials.gov.

Results—Only 5% of the 107 pharmacological trials for depression published in 2007 reported the smoking status of their samples. Two studies (1.9%) controlled for smoking in the analyses and no studies analyzed outcomes by smoking status. Excluding the 8 studies of combined treatment for depression and nicotine dependence, no other study on www.Clinicaltrials.gov (total n=920) reported an intention to analyze outcomes by smoking status.

Discussion—Emerging data link smoking and depression, however, little attention has been directed toward the effects of smoking on antidepressant treatment outcomes. Conducting research to understand how nicotine and smoking affect responsiveness to antidepressants would advance our understanding of the neurobiology of depression and the development of new and targeted treatments.

Keywords

depression; smoking; clinical trials; treatment; review

INTRODUCTION

Major depression is one of the greatest causes of disability throughout the world (Murray 1997), and one of the most common psychiatric illnesses in the United States with a lifetime prevalence of 16.2% and a 12-month prevalence of 6.6% (Kessler et al., 2003). The effects of depression are wide-reaching and include increased morbidity and mortality, diminished functioning, treatment expenditures, increased work absenteeism and impaired work

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Conflicts of Interest

Drs. Weinberger, McKee, Picciotto, and Mazure declare they have no conflicts to report.

performance (Broadhead et al., 1990; Kessler et al., 2003; Klerman and Weissman, 1992; Luppá et al., 2007; Wang et al., 2008), all of which add up to billions of dollars of societal costs each year (Greenberg et al., 2003). While interventions can improve psychological well-being, health, and work performance (Wang et al., 2008), a significant proportion of patients do not receive adequate treatment for depression (Kessler et al., 2003). Even when patients do receive treatment, a sizable number do not find relief from depressive symptoms with the use of FDA-approved antidepressant pharmacotherapies (Mathew and Charney, 2009). Identifying and studying factors associated with non-response to antidepressants can help in the development of novel or targeted treatments that reach the greatest number of those with depression.

Although smoking and depression have been linked through epidemiological, neurobiological, and clinical research, the effects of smoking on antidepressant treatment outcomes have rarely been examined. The purpose of this report is to: 1) consider why it is important to examine the relationship between smoking and antidepressant treatment outcome and 2) examine the extent to which smoking status is considered in current clinical trial research on antidepressant agents.

The relationship between smoking and depression

Adults with depression are much more likely to smoke than adults in the general population (36.6% versus 22%; Husky et al., 2008; Lasser et al., 2000). Nicotine dependence, which is defined as daily smoking, lack of aversive effects from nicotine (e.g., nausea), and the presence of withdrawal symptoms upon smoking cessation (e.g., cravings, anxiety, dysphoria, increased appetite) (APA 1994), is also more likely to be found in adults with depression than nondepressed adults (30% versus 12.8%; Dierker and Donny, 2008; Grant et al., 2004). The presence of depression has been linked to difficulty with smoking cessation and increased smoking relapse (Anda et al., 1990; Glassman et al., 1990; Kinnunen et al., 1999; Walsh et al., 2008; Wilhelm et al., 2006) and smoking cessation may precipitate new depressive episodes for smokers with a history of depression (Glassman et al., 2001). Conversely, smokers report greater symptoms of depression, more frequent episodes of depression, and higher rates of suicidal ideation and suicide than nonsmokers (Wilhelm et al., 2006). Although there have also been conflicting findings (e.g., Hitsman et al., 2003; Niaura et al., 1999; see Ziedonis et al., 2008 for review), a number of studies report that smokers with depression have a more difficult time quitting smoking and avoiding relapse (e.g., Kinnunen et al., 1999; Walsh et al., 2008; Wilhelm et al., 2006).

The role of nicotinic acetylcholine receptors in smoking, depression, and antidepressant response

Nicotinic acetylcholine receptors (nAChRs), located throughout the brain and soma, are the primary target of nicotine in the brain and modulate pathways involved in response to stress and depression (Picciotto et al., 2008; Picciotto et al., 2002). Through nAChRs, nicotine modulates multiple neurotransmitters (e.g., serotonin, dopamine, acetylcholine), and chronic nicotine exposure results in changes to nAChRs including receptor desensitization and upregulation of nicotine binding sites (Picciotto et al., 2008; Picciotto et al., 2002).

Animal models—A growing body of research using standardized animal models of depression (e.g., the forced swim test (FST), the tail suspension test (TST), and the learned helplessness paradigm (LH); see Cryan et al., 2005a,b; Thiebot et al., 1992 for reviews) has reported that both nicotinic agonists and antagonists show antidepressant effects, an apparently conflicting finding which has been attributed to the complicated pattern of desensitization and activation of different nAChR subunits (Picciotto et al., 2008). Specifically, antidepressant effects have been found with the administration of nicotine, the

nicotinic antagonist mecamylamine, the nicotinic partial agonist cytisine, and the nicotinic agonist SIB-1508Y (atinicline) (see Table 1). The positive effect of nicotinic agents on depressive response in preclinical models is similar in magnitude to what is demonstrated with a variety of antidepressant agents (see Table 1). Furthermore, mice lacking high-affinity nAChRs display no antidepressant response to amitriptyline suggesting that nAChRs are, in fact, necessary for the therapeutic action of antidepressants (see Picciotto et al., 2008 for review).

Preclinical data also indicate that several FDA-approved antidepressants, shown to be noncompetitive nAChR antagonists (e.g., imipramine, amitriptyline, fluoxetine, citalopram; see Shytle et al., 2002a for review), can be potentiated by the co-administration of nicotine or mecamylamine. For example, using the same animal model (TST), imipramine (Steru et al., 1985), and the nicotinic agents cytisine (Mineur et al., 2007), and mecamylamine (Mineur 2007), each induced antidepressant responses with large effect sizes ($d=1.72, 1.94, 2.35$, respectively) and, when imipramine was coadministered with either nicotine or mecamylamine (Popik et al., 2003), the combination improved antidepressant response relative to imipramine alone ($d=1.02, 1.10$ respectively, see Tables 1–2).

Clinical research—It has been suggested that adults with depression smoke in part to reduce depressive or negative affect (McKee et al., 2003a,b) and, in fact, smokers with depression are more likely than other smokers to report smoking to relieve negative affect (Kinnunen et al., 1999; McKee et al., 2003b; Wilhelm et al., 2006). Although nicotinic agents have been suggested as novel treatments for depression based on the preclinical findings presented above (George et al., 2008; Laje et al., 2001; Picciotto et al., 2002; Shytle et al., 2002a), few studies have examined the relationship of nicotine or nicotinic agents and depressive symptoms in human laboratory studies or clinical trials. However, the studies that have examined nicotinic agents on depressive symptoms in humans have been encouraging (e.g., George et al., 2008; Philip et al., 2009; Shytle et al., 2002b; see Table 3). The administration of nicotine through a transdermal nicotine patch has been linked to improved mood in smoking and nonsmoking adults (Laje et al., 2001; McClernon et al., 2006; Salin-Pascual et al., 1996). There is preliminary evidence that mecamylamine reduces depression and irritability in children and adolescents with co-morbid Tourette's Disorder and major depression (Shytle et al., 2002b) and that mecamylamine and varenicline reduce depression in antidepressant-treated adults with current symptoms of depression (George et al., 2008; Philip et al., 2009). The pharmaceutical company Targacept, Inc has also reported positive results from two studies of adults with depression who received either mecamylamine (Targacept, 2007; ClinicalTrials.gov Identifier NCT00593879) or the nicotinic antagonist TC-5214 (Targacept, 2009; ClinicalTrials.gov Identifier NCT00692445), which had shown antidepressant properties in preclinical research (Lippiello et al., 2008), as an adjunct to citalopram.

Would smokers and nonsmokers be expected to differ in their response to antidepressants?

While smoking has been found to be linked to depression through epidemiological and neurobiological research, the effects of smoking on treatment outcomes have been rarely examined and it is therefore unclear whether adult smokers differ from adult nonsmokers in their response to antidepressant medications. While adults with depression exhibited a greater decrease in symptoms with a combination of an SSRI and mecamylamine than an SSRI alone (George et al., 2008), secondary analysis showed that smokers responded less well than nonsmokers to the combination. Because antidepressants work in part through nAChRs and chronic nicotine exposure results in nAChR receptor changes including receptor desensitization and upregulation of binding sites (Picciotto et al., 2008), differential

response to mecamylamine by smoking status may have been due to smoking-related changes in nAChR function. If so, this suggests that while nAChRs antagonists may be a useful adjunct to antidepressant pharmacotherapies, adult smokers with depression may respond differently to such treatments. While nicotine might enhance response to antidepressants, the nAChR system is complex and smoking-related changes in the system might alter the functionality of nAChR agents in a positive or negative direction. The complexity of this relationship (Picciotto et al., 2002) highlights the importance of conducting controlled research to understand how nicotine affects nAChRs and responsiveness to antidepressant medications (Picciotto et al., 2008).

Aims of the current review

The purpose of this review is to examine the frequency with which contemporary clinical trials of antidepressant agents include information about the smoking status of participants, control analyses for smoking status, or analyze outcomes by smoking status. We reviewed all pharmacological trials of depression published during the year 2007 listed in MEDLINE, and all interventional studies for depression listed on Clinicaltrials.gov. It was expected that a minority of these studies would report baseline smoking status or examine treatment outcomes by smoking status.

METHODS AND MATERIALS

Study Design

We first conducted a MEDLINE search of recent randomized clinical trials of pharmacotherapy for depression published between January 1 and December 31, 2007. Data on the journal of publication, type of funding, and sample size were collected from each paper. Each article was classified (yes/no) as to whether it (1) reported the rate of smoking in the sample, (2) examined trial outcomes by smoking status, (3) included smoking status as a covariate in the analyses, and (4) reported smoking rates at the end of the clinical trial.

To further examine the inclusion of smoking status in clinical trials of depression using the most current data available, we conducted a second search on Clinicaltrials.gov. The Clinicaltrials.gov website (<http://www.Clinicaltrials.gov>) is a registry of over 68,000 clinical trials conducted in the United States and around the world. U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007; FDAAA), Title VIII, Section 801 mandates that clinical trials of drugs, biologics, and devices be registered at Clinicaltrials.gov. Clinicaltrials.gov was accessed on February 9, 2009 and a search was conducted using the terms “interventional study” and “depression.” The records identified through this search were individually examined to determine whether smoking status was listed as part of the inclusion or exclusion criteria, study design, or analysis plan.

RESULTS

Results of the MEDLINE search

Of 222 original articles published during 2007, 72 were excluded because they were not randomized clinical trials ($n=53$), were trials of a condition other than depression ($n=13$), or were not published in English ($n=6$). An additional 43 studies were excluded because they were clinical trials only of behavioral treatments for depression (i.e., no pharmacological treatments were provided). The 107 randomized clinical trials of pharmacological treatments for depression that were included in the review were published in 74 different journals.

Within the 107 pharmacological trials, sample sizes ranged from 18 to 4,041 participants (mean=338; standard deviation=586). The majority of articles focused on a subpopulation

with depression including patients with a medical disorder (e.g., patients with stroke or chronic obstructive pulmonary disease; $n=16$), older or geriatric adults ($n=13$), patients with a co-morbid psychiatric or substance use disorder ($n=14$), and adolescents ($n=7$). Studies were split between those examining pharmacological treatments alone (58%) and those examining a combination of pharmacological and behavioral treatments (42%). Twenty-four percent of the studies reported receiving funding from the National Institutes of Health (NIH), 58% reported funding from other sources (e.g., pharmaceutical companies), and 18% did not list the source of funding.

The majority of studies ($n=102$; 95.3%) did not report the rates of smoking in their samples. Within the five studies that reported smoking status, the percent of smokers ranged from 4% to 60% (mean=30%). Two studies (1.9%) controlled for smoking in their analyses. No study included smoking as a variable in their analysis and no study reported the smoking status of their participants at the end of the clinical trial.

Results of the Clinicaltrials.gov search

At the time that ClinicalTrials.gov was accessed, there were nine hundred and twenty studies registered as interventional studies of depression (including Phase I, II, III, and IV studies). Of these 920 studies, 8 studies reported a focus on combined treatment for both nicotine dependence and depression, 3 studies listed smoking or nicotine dependence as criteria for exclusion, and one study stated under their inclusion criteria that both smokers and nonsmokers could participate. Twelve additional studies reported that they would exclude participants with substance dependence “not including nicotine.” Excluding the 8 studies of combined treatment for smoking and depression, no other study reported an intention to analyze outcomes by smoking status.

DISCUSSION

The current study examined the frequency at which smoking status is reported and considered in treatment outcomes in pharmacotherapy trials for depression published during the year 2007 and in interventional studies listed on Clinicaltrials.gov. Both reviews showed that studies for depression are not analyzing outcomes by smoking status to determine whether smokers and nonsmokers show a differential response to antidepressant medication. Epidemiological and neurobiological evidence indicate a strong link between smoking and depression. Both smoking and depression affect the nAChR system and a significant amount of preclinical research has found that nicotinic agents exert antidepressant effects in traditional models of depression in animals. Many antidepressants have affinity for nAChRs, and nAChRs have been proposed as potential therapeutic targets for depression (e.g., Laje et al., 2001; Picciotto et al., 2002; Shytle et al., 2002a). Preclinical research has shown that nicotinic agents modify the effects of FDA-approved antidepressants and clinical research has offered preliminary research that augmenting antidepressant treatment with nicotinic agents improves the outcomes for treatment-resistant adults with depression.

While evidence discussed above suggests that nAChR agents including varenicline might have antidepressant properties, there has been significant controversy regarding whether varenicline increases suicidal ideation in smokers trying to quit. These concerns have led the FDA to issue a black box warning for varenicline. A recent report (Tonstad et al., 2010) that examined all controlled clinical trials of varenicline for smoking cessation on record with the pharmaceutical manufacturer (Pfizer, Inc) found no increase in psychiatric disorders (including suicidal ideation or behavior) for participants receiving varenicline ($n=3,091$) compared to participants receiving placebo ($n=2,005$). Further, an examination of 80,660 adults in the United Kingdom found no increase in depression, suicidal thoughts, or self-harm for participants receiving varenicline as compared to nicotine replacement therapy or

bupropion (Gunnell et al., 2009). Because smoking is associated with an increased risk of suicidal behavior (Wilhelm et al., 2006) and smoking cessation may lead to episodes of depression in smokers with a history of depression (Glassman et al., 2001; Glassman et al., 1990), symptoms of depression including suicidal ideation should be monitored closely during any quit attempt whether it is done as part of a clinical research trial or in a clinical setting. Monitoring of suicidal symptoms should be conducted with a validated and treatment-sensitive measure, such as the Sheehan Suicide Tracking Scale (Coric et al., 2009).

While nicotine might enhance response to antidepressants, the nAChR system is complex and smoking-related changes in the system might alter the functionality of nAChR agents in a positive or negative direction (Picciotto et al., 2008). Current questions concerning the efficacy of antidepressants (Mathew and Charney, 2009) and the controversy regarding varenicline and suicidal behavior highlight the importance of conducting controlled research to understand how nicotine affects nAChRs and responsiveness to antidepressant medications. Research is needed to understand whether and what type of effects smoking has on depression in antidepressant treatment outcomes. Nonetheless, the very low rate at which smoking status of study participants is reported (<5% of studies published in 2007) suggests that the effects of smoking are rarely considered in assessing antidepressant outcome. Such knowledge would advance our understanding of the neurobiology of depression and the development of new and targeted treatments.

Several limitations of the current study must be acknowledged. Because only published studies from the year 2007 were reviewed, it is unclear whether the attention to smoking in depression research has increased or decreased over time. In addition, the authors were only able to include clinical trials in the review that were published and accessible on MEDLINE. Research has found that studies of antidepressant medications with negative findings are more likely to not be published than studies with positive outcomes (Turner et al., 2008). In terms of information reported through Clinicaltrials.gov postings, although the registry requires researchers to describe the planned primary and secondary analyses and provide a summary of each study, it does not specifically compel researchers to provide information about all assessed variables. Consequently, it is possible that some researchers assess smoking status but do not report this information. Nonetheless, the very low rate at which smoking status of study participants is reported suggests that the effects of smoking are rarely considered in assessing antidepressant outcome.

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References

- Anda RF, Williamson DF, Escobedo LG, Mast EE, Giovino GA, Remington PL. Depression and the dynamics of smoking: A national perspective. *JAMA*. 1990; 264:1541–1545. [PubMed: 2395193]
- APA. Diagnostic and statistical manual of mental disorders. 4. Washington DC: American Psychiatric Association; 1994.

- Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. *JAMA*. 1990; 264:2524–2528. [PubMed: 2146410]
- Caldarone BJ, Harrist A, Cleary MA, Beech RD, King SL, Picciotto MR. High-affinity nicotinic acetylcholine receptors are required for antidepressant effects of amitriptyline on behavior and hippocampal cell proliferation. *Biol Psychiatry*. 2004; 56:657–664. [PubMed: 1552249]
- Caldarone BJ, Karthigeyan K, Harrist A, Hunsberger JG, Wittmack E, King SL, Jatlow P, Picciotto MR. Sex differences in response to oral amitriptyline in three animal models of depression in C57BL/6J mice. *Psychopharmacology*. 2003; 170:94–101. [PubMed: 12879206]
- Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, N.J.: Lawrence Erlbaum Associates; 1988.
- Coric V, Stock EG, Pultz J, Marcus R, Sheehan DV. Sheehan Suicidality Tracking Scale (Sheehan-STS): Preliminary results from a multicenter clinical trial in generalized anxiety disorder. *Psychiatry (Edmont)*. 2009; 6:26–31. [PubMed: 19724740]
- Cryan JF, Mombereau C, Vassout A. The tail suspension test as a model for assessing antidepressant activity: Review of pharmacological and genetic studies in mice. *Neurosci Biobehav Rev*. 2005a; 29:571–625. [PubMed: 15890404]
- Cryan JF, Valentino RJ, Lucki I. Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. *Neurosci Biobehav Rev*. 2005b; 29:547–569. [PubMed: 15893822]
- Dierker L, Donny E. The role of psychiatric disorders in the relationship between cigarette smoking and DSM-IV nicotine dependence among young adults. *Nicotine Tob Res*. 2008; 10:439–446. [PubMed: 18324562]
- Djuric VJ, Dunn E, Overstreet DH, Dragomir A, Steiner M. Antidepressant effects of ingested nicotine and female rats of finders resistant and sensitive lines. *Phys Behav*. 1999; 67:533–537.
- Ferguson SM, Brodtkin JD, Lloyd GK, Menzaghi F. Antidepressant-like effects of the subtype-selective nicotinic acetylcholine receptor agonist, SIB-1508Y, in the learned helplessness rat model of depression. *Psychopharmacology*. 2000; 152:295–303. [PubMed: 11105940]
- George TP, Sacco KA, Vessicchio JC, Weinberger AH, Shytle RD. Nicotinic antagonist augmentation of selective serotonin reuptake inhibitor-refractory major depressive disorder: A preliminary study. *Journal Clin Psychopharmacol*. 2008; 28:340–344.
- Glassman AH, Covey LS, Stetner F, Rivelli S. Smoking cessation and the course of major depression: A follow-up study. *Lancet*. 2001; 357:1929–1932. [PubMed: 11425414]
- Glassman AH, Helzer JE, Covey LS, Cottler LB, Stetner F, Tipp JE, Johnson J. Smoking, smoking cessation and major depression. *JAMA*. 1990; 264:1546–1549. [PubMed: 2395194]
- Grant BF, Hasin DS, Chou P, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States. *Arch Gen Psychiatry*. 2004; 61:1107–1115. [PubMed: 15520358]
- Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey-Lisle PK. The economic burden of depression in the United States: How did it change between 1990 and 2000? *J Clin Psychiatry*. 2003; 64:1465–1475. [PubMed: 14728109]
- Gunnell D, Irvine D, Wise L, Davies C, Martin RM. Varenicline and suicidal behaviour: A cohort study based on data from the General Practice Research Database. *BMJ*. 2009; 339:b3805. [PubMed: 19797344]
- Hitsman B, Borrelli B, McChargue DE, Spring B, Niaura R. History of depression and smoking cessation outcome: A meta-analysis. *J Consult Clin Psychol*. 2003; 71:657–663. [PubMed: 12924670]
- Husky MM, Mazure CM, Paliwal P, McKee SA. Gender differences in the comorbidity of smoking behavior and major depression. *Drug Alcohol Depend*. 2008; 93:176–179. [PubMed: 17850991]
- Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003; 289:3095–3105. [PubMed: 12813115]
- Kinnunen T, Henning L, Nordstrom BL. Smoking cessation in individuals with depression: Recommendations for treatment. *CNS Drugs*. 1999; 11:93–103.

- Klerman GL, Weissman MM. The course, morbidity, and costs of depression. *Arch Gen Psychiatry*. 1992; 49:831–834. [PubMed: 1417437]
- Laje RP, Berman JA, Glassman AH. Depression and nicotine: Preclinical and clinical evidence for common mechanisms. *Curr Psychiatry Rep*. 2001; 3:470–474. [PubMed: 11707160]
- Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *JAMA*. 2000; 284:2606–2610. [PubMed: 11086367]
- Lippiello PM, Beaver JS, Gatto GJ, James JW, Jordan KG, Traina VM, Xie J, Bencherif M. TC-5214 (S-(+)-mecamylamine): A neuronal nicotinic receptor modulator with antidepressant activity. *CNS Neurosci Ther*. 2008; 14:266–277. [PubMed: 19040552]
- Lucki I, Dalvi A, Mayorga AJ. Sensitivity to the effects of pharmacologically selective antidepressants in different strains of mice. *Psychopharmacology*. 2001; 155:315–322. [PubMed: 11432695]
- Luppa M, Heinrich S, Angermeyer MC, König HH, Riedel-Heller SG. Cost-of-illness studies of depression: A systematic review. *J Affect Disorders*. 2007; 98:29–43. [PubMed: 16952399]
- Mathew SJ, Charney DS. Publication bias and the efficacy of antidepressants. *Am J Psychiatry*. 2009; 166:140–145. [PubMed: 19188290]
- McCleron FJ, Hiott FB, Westman EC, Rose JE, Levin ED. Transdermal nicotine attenuates depression symptoms in nonsmokers: A double-blind, placebo-controlled trial. *Psychopharmacology*. 2006; 189:125–133. [PubMed: 16977477]
- McKee SA, Maciejewski PK, Falba T, Mazure CM. Sex differences in the effects of stressful life events on changes in smoking status. *Addiction*. 2003a; 98:847–855. [PubMed: 12780373]
- McKee SA, Wall A-M, Hinson RE, Goldstein A, Bissonnette M. Effects of an implicit mood prime on the accessibility of smoking expectancies in college women. *Psychol Addict Behaviors*. 2003b; 17:219–225.
- Mineur YS, Somenzi O, Picciotto MR. Cytisine, a partial agonist of high-affinity nicotinic acetylcholine receptors, has antidepressant-like properties in male C57BL/6J mice. *Neuropharmacology*. 2007; 52:1256–1262. [PubMed: 17320916]
- Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet*. 1997; 349:1498–1504. [PubMed: 9167458]
- Niaura R, Britt DM, Borrelli B, Shadel WG, Abrams DB, Goldstein MG. History and symptoms of depression among smokers during a self-initiated quit attempt. *Nicotine Tob Res*. 1999; 1:251–257. [PubMed: 11072422]
- Philip NS, Carpenter LL, Tyrka AR, Whiteley LB, Price LH. Varenicline augmentation in depressed smokers: An 8-week, open-label study. *J Clin Psychiatry*. 2009; 70:1026–1031. [PubMed: 19323966]
- Picciotto MR, Addy NA, Mineur YS, Brunzell DH. It is not “either/or”: Activation and desensitization of nicotinic acetylcholine receptors both contribute to behaviors related to nicotine addiction and mood. *Prog Neurobiol*. 2008; 84:329–342. [PubMed: 18242816]
- Picciotto MR, Brunzell DH, Caldarone BJ. Effect of nicotine and nicotinic receptors on anxiety and depression. *NeuroReport*. 2002; 13:1097–1106. [PubMed: 12151749]
- Popik P, Kozela E, Krawczyk M. Nicotine and nicotinic receptor antagonists potentiate the antidepressant-like effects of imipramine and citalopram. *Brit J Pharmacol*. 2003; 139:1196–1202. [PubMed: 12871839]
- Rabenstein RL, Caldarone BJ, Picciotto MR. The nicotinic antagonist mecamylamine has antidepressant-like effects in wild-type but not $\alpha 2$ - or $\alpha 7$ -nicotinic acetylcholine receptor subunit knockout mice. *Psychopharmacology*. 2006; 189:395–401. [PubMed: 17016705]
- Salin-Pascual RJ, Rosas M, Jimenez-Genchi A, Rivera-Meza BL, Delgado-Parra V. Antidepressant effect of transdermal nicotine patches in non-smoking patients with major depression. *J Clin Psychiatry*. 1996; 57:387–389. [PubMed: 9746444]
- Shytle RD, Silver AA, Lukas RJ, Newman MB, Sheehan DV, Sanberg PR. Nicotinic acetylcholine receptors as targets for antidepressants. *Mol Psychiatry*. 2002a; 7:525–535. [PubMed: 12140772]
- Shytle RD, Silver AA, Sheehan KH, Sheehan DH, Sanberg PR. Neuronal nicotinic receptor inhibition for treating mood disorders: preliminary controlled evidence with mecamylamine. *Depress Anxiety*. 2002b; 16:89–92. [PubMed: 12415531]

- Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: A new method for screening antidepressants in mice. *Psychopharmacology*. 1985; 85:367–370. [PubMed: 3923523]
- Takeuchi H, Yatsugi S, Hatanaka K, Nakato K, Hattori H, Sonoda R, Koshiya K, Fujii M, Yamaguchi T. Pharmacological studies on YM992, a novel antidepressant with selective serotonin re-uptake inhibitory and 5-HT receptor 2A antagonistic activity. *Eur J Pharmacology*. 1997; 329:27–35.
- Targacept. Targacept presents data from tridmac trial showing positive effects of mecamylamine as augmentation treatment for depressed patients. 2007 July 24. Retrieved from http://www.drugs.com/clinical_trials/targacept-presents-data-tridmac-trial-showing-positive-mecamylamine-augmentation-depressed-patients-1643.html
- Targacept. Targacept presents data from highly successful phase 2b trial of TC-5214 as augmentation treatment for major depressive disorder. 2009 October 15. Retrieved from http://www.targacept.com/wt/page/pr_1255642681
- Thiebot MH, Martin P, Puech AJ. Animal behavioural studies in the evaluation of antidepressant drugs. *Br J Psychiatry Supp*. 1992; 15:44–50.
- Tizabi Y, Rezvani AH, Russell LT, Tyler KY, Overstreet DH. Depressive characteristics of FSL rats: Involvement of central nicotinic receptors. *Pharmacol Biochem Behav*. 2000; 66:73–77. [PubMed: 10837845]
- Tonstad S, Davies S, Flammer M, Russ C, Hughes J. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of Varenicline: A pooled analysis. *Drug Safety*. 2010; 33:289–301. [PubMed: 20297861]
- Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med*. 2008; 358:252–260. [PubMed: 18199864]
- Vazquez-Palacios G, Bonilla-Jaime H, Velazquez-Moctezuma J. Antidepressant-like effects of the acute and chronic administration of nicotine in the rat forced swimming test and its interaction with fluoxetine. *Pharmacol Biochem Behav*. 2004; 78:165–169. [PubMed: 15159146]
- Vazquez-Palacios G, Bonilla-Jaime H, Velazquez-Moctezuma J. Antidepressant effects of nicotine and fluoxetine in an animal model of depression induced by neonatal treatment with clomipramine. *Prog in Neuro-Psychopharmacol*. 2005; 29:39–46.
- Walsh Z, Epstein A, Munisamy G, King A. The impact of depressive symptoms on the efficacy of naltrexone in smoking cessation. *J Addict Dis*. 2008; 27:65–72. [PubMed: 18551889]
- Wang PS, Simon GE, Kessler RC. Making the business case for enhanced depression care: the National Institute of Mental Health-Harvard work outcomes research and cost-effectiveness study. *J Occup Environ Med*. 2008; 50:468–475. [PubMed: 18404020]
- Wedgwood L, Niven H, Kay-Lambkin F, Wilhelm Consultation Liaison Psychiatry. Smoking cessation and depression: current knowledge and future directions. *Drug Alcohol Rev*. 2006; 25:97–107. [PubMed: 16492582]
- Ziedonis D, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, Breslau N, Brown RA, George TP, Williams J, Calhoun PS, Riley WT. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine Tob Res*. 2008; 10:1691–1715. [PubMed: 19023823]

Table 1
Effects of antidepressant agents, nicotine, nicotinic agents, and nicotinic receptor knockouts in animal models of depression

Author	Antidepressant Class	Antidepressant Agent, Nicotine, Nicotinic Agent, or Knock-out	Administration	Test	Dependent Measure	Effect size ^a
Steru et al., 1985	TCA	amitriptyline	60 minutes	TST	Immobility	d=1.68
Caldarone et al., 2003	TCA	amitriptyline	4, 21 days	TST	Immobility	d=1.08
			21 days	FST	Immobility	d=0.29
			4, 21 days	LH	Escape latencies	d=0.70 to 1.12
Steru et al., 1985	TCA	imipramine	30 minutes	TST	Immobility	d=1.72
Ferguson et al., 2000	TCA	imipramine	5 days	LH	Escape failure	d=0.55
Takeuchi et al., 1997	SSRI	citalopram	48 minutes	TST	Immobility	d=4.67*
Ferguson et al., 2000	SSRI	fluoxetine	5 days	LH	Escape failure	d=0.54
Lucki et al., 2001	SSRI	fluoxetine	30 minutes	FST	Immobility	d=0.55 to 0.66
Vazquez-Palacios et al., 2005	SSRI	fluoxetine	7 days	FST	Immobility	d=0.24
					Swimming	d=0.24
					Climbing	d=0.24
			14 days	FST	Immobility	d=0.24
					Swimming	d=0.24
Djuric et al., 1999	---	nicotine	14 days	FST	Immobility	d=0.73
			10 minutes	FST	Immobility	d=1.08
			14 days	FST	Immobility	d=1.32
Tizabi et al., 2000	---	nicotine	5 days	LH	Escape failure	d=0.87
Ferguson et al., 2000	---	nicotine	10 minutes	FST	Immobility	d=0.71
Vazquez-Palacios et al., 2004	---	nicotine	10 minutes	FST	Swimming	d=0.74
					Climbing	d=0.36
					Immobility	d=0.83
			7 days	FST	Swimming	d=0.87
					Climbing	d=0.39
			14 days	FST	Immobility	d=0.80

Author	Antidepressant Class	Antidepressant Agent, Nicotine, Nicotinic Agent, or Knock-out	Administration	Test	Dependent Measure	Effect size ^a
Vazquez-Palacios et al., 2005	---	nicotine	1 day	FST	Swimming	d=0.89
					Immobility	d=0.54
					Swimming	d=0.22
					Climbing	d=0.13
					Immobility	d=0.40
	---	nicotine	7 days	FST	Swimming	d=0.22
					Climbing	d=0.13
					Immobility	d=0.24
					Swimming	d=0.24
					Climbing	d=0.15
Mineur et al., 2007	---	cytosine	15 minutes	TST	Immobility	d=1.94
				FST	Immobility	d=1.16
Caldarone et al., 2004	---	mecamylamine	30 minutes	FST	Immobility	d=1.24
Rabenstein et al., 2006	---	mecamylamine	30 minutes	TST	Immobility	d=0.67
				FST	Immobility	d=1.11
Mineur et al., 2007	---	mecamylamine	15 minutes	TST	Immobility	d=2.35
				FST	Immobility	d=1.18
Ferguson et al., 2000	---	SIB-1508Y	5 days	LH	Escape failure	d=1.16
Rabenstein et al., 2006	---	$\alpha 7$ KO	---	FST	Immobility	d=0.79
		$\beta 2$ KO	---	FST	Immobility	d=0.66
Caldarone et al., 2004	---	$\beta 2$ KO	---	TST	Immobility	d=1.48
				FST	Immobility	d=1.06

Key: TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitors; LH, learned helplessness; TST, tail suspension test; FST, forced swim test; KO, knock-out

Note: Based on information provided in the text of each article, the authors calculated effect sizes using Cohen's *d* (Cohen, 1988). Classification of Effect Sizes: Large effect size, $d \geq 0.75$; Medium effect size, $d \geq 0.40$ and < 0.75 ; Small effect size, $d \geq 0.15$ and < 0.40 ; Negligible effect size, $d < 0.15$.

* Estimated from mean and standard deviation.

^a All effect sizes are based on results demonstrating that the antidepressant agent, nicotine, nicotinic agents, or knock-out improved dependent measures in animal models of depression greater than placebo.

Table 2

Potiation of effects when nicotine, nicotinic agents, or nicotinic receptor knockouts are combined with antidepressant agents in animal models of depression

Author	Antidepressant Class	Antidepressant Agent	Administration	Nicotinic Agent or Knockout	Administration	Test	Dependent Measure	Effect size
Caldarone et al., 2004	TCA	amitriptyline	21 days	Mecamylamine	30 minutes	FST	Immobility	d=1.59 ^a
				KO ($\beta 2$)	---	FST	Immobility	d=0.66 ^b
Popik et al., 2003	TCA	imipramine	30 minutes	Nicotine	15 minutes	TST	Immobility	d=1.02 ^b
				Mecamylamine	40 minutes	TST	Immobility	d=1.10 ^b
Popik et al., 2003	SSRI	citalopram	30 minutes	Nicotine	15 minutes	TST	Immobility	d=1.02 ^b
				Mecamylamine	40 minutes	TST	Immobility	d=0.93 ^b
Vazquez- Palacios et al., 2005	SSRI	fluoxetine	1 day	Nicotine	1 day	FST	Immobility	d=0.55 ^a
						FST	Swimming counts	d=0.22 ^a
			7 days	Nicotine	7 days	FST	Immobility	d=0.24 ^a
						FST	Swimming counts	d=0.24 ^a
			14 days	Nicotine	14 days	FST	Immobility	d=0.24 ^a
						FST	Swimming counts	d=0.24 ^a

Key: TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitors; KO, knockout; LH, learned helplessness; TST, tail suspension test; FST, forced swim test

Note: Based on information provided in the text of each article, the authors calculated effect sizes using Cohen's *d* (Cohen, 1988). Classification of Effect Sizes: Large effect size, $d \geq 0.75$; Medium effect size, $d \geq 0.40$ and < 0.75 ; Small effect size, $d \geq 0.15$ and < 0.40 ; Negligible effect size, $d < 0.15$.

^a All effect sizes are based on results demonstrating that the combination of antidepressant agent + nicotine, nicotinic agent, or knockout improved dependent measures in animal models of depression greater than placebo.

^b All effect sizes are based on results demonstrating that the combination of antidepressant agent + nicotine, nicotinic agent, or knockout additively improved dependent measures in animal models of depression greater than the antidepressant alone.

Table 3

Effects of nicotine on symptoms of depression in humans

Author	Agent	Administration	Test	Effect size ^a
Salin-Pascual et al., 1996	transdermal nicotine patch	2 days	HDRS (10 item)	d=4.03 [*]
McCleron et al., 2006	transdermal nicotine patch	8 days	CES-D	d=2.33
			POMS-Bi	d=2.30
George et al., 2008	mecamylamine ^b	56 days	HDRS (17 item)	d=1.17

Key: CES-D, Center for Epidemiologic Studies Depression Scale; POMS, The Profile of Mood States-Bipolar (elated-depressed scale); HDRS, Hamilton Depression Rating Scale, 10 item

Notes: Based on information provided in the text of each article, the authors calculated effect sizes using Cohen's d (Cohen, 1988). Classification of Effect Sizes: Large effect size, $d \geq 0.75$; Medium effect size, $d \geq 0.40$ and < 0.75 ; Small effect size, $d \geq 0.15$ and < 0.40 ; Negligible effect size, $d < 0.15$. For two other references cited in the text (Laje et al., 2001; Shytle et al., 2002b), it was not possible to calculate an effect size. Philip et al. (2009) was an open-label study of varenicline and therefore an effect size compared to placebo could not be calculated.

^{*} Estimated from mean and standard deviation.

^a All effect sizes are based on results demonstrating that transdermal nicotine patch or mecamylamine resulted in greater reduction of depression symptoms than placebo patch or placebo pill.

^b Mecamylamine or placebo pill were administered in conjunction with a selective serotonin reuptake inhibitor.