DR SEETAL DODD (Orcid ID : 0000-0002-7918-4636)

Article type : Review of Therapeutics

Title: Current and Emerging Pharmacotherapies for Cessation of Tobacco Smoking

Authors:

Nieves Gómez-Coronado¹, Adam J. Walker², Michael Berk^{2,3,4,5,6}, Seetal Dodd^{2,3,4,5}

Author affiliations:

¹ Unidad de Gestión Clínica Salud Mental, Hospital Universitario Virgen del Rocío, Sevilla, Spain

² Deakin University, Geelong, IMPACT Strategic Research Centre, VIC, Australia

³ University Hospital Geelong, Barwon Health, Geelong VIC Australia

⁴ Department of Psychiatry, The University of Melbourne, Parkville, VIC, Australia

⁵ Orygen, the National Centre of Excellence in Youth Mental Health, Parkville, VIC, Australia

⁶ Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia

Key words: smoking cessation, tobacco cessation, nicotine dependence, pharmacotherapy.

Correspondence to: Seetal Dodd, IMPACT Strategic Research Centre, School of Medicine, Deakin University, P.O. Box 291, Geelong, 3220, Australia.

Email: seetald@barwonhealth.org.au

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/phar.2073](https://doi.org/10.1002/phar.2073)

This article is protected by copyright. All rights reserved

Conflict of interest: AJW and NGC have no conflicts of interest. MB has received grant/research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier and Woolworths, has been a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck Merck, Pfizer and Servier. SD has received grants/research support from the Stanley Medical Research Institute, NHMRC, Beyond Blue, ARHRF, Simons Foundation, Geelong Medical Research Foundation, Fondation FondaMental, Eli Lilly, Glaxo SmithKline, Organon, Mayne Pharma and Servier, speaker's fees from Eli Lilly, advisory board fees from Eli Lilly and Novartis, and conference travel support from Servier.

RRH: Pharmacotherapies for Cessation of Tobacco Smoking

Abstract

Tobacco use disorder is a chronic illness. With its high comorbidity rate, it is a major cause of years of life lost or years lived with disability; however, is also considered the most preventable cause of death in developed countries. Since the development of nicotine replacement therapy (NRT) in 1978, treatment options have continued to evolve and expand. Despite this, currently available treatments remain insufficient, with less than 25% of smokers remaining abstinent after one year after treatment. In this article, we review existing and emerging smoking cessation pharmacotherapies, affording a special emphasis on the most promising agents that are currently being investigated. A search of the Cochrane Database of Systematic Reviews and the PubMed, OVID, and ClinicalTrials.gov databases (2 August to 1 September 2017) was undertaken for articles on smoking cessation pharmacotherapies, applying no language restrictions. Over 40 pharmacotherapies are reviewed, including conventional pharmacotherapies—NRT, bupropion, and varenicline (all approved by the United States Food and Drug Administration as first-line treatment of smoking cessation)—and novel therapies—cystisine, *N*-acetylcysteine, cycloserine, memantine, baclofen, topiramate, galantamine, and bromocriptine. Studies of combination NRT and varenicline showed the greatest smoking cessation rates. Clonidine and nortriptyline are second-line treatments that are used when first-line treatments fail or are contraindicated, or by

patient preference. Some novel therapies, especially acetylcholinesterase inhibitors, cytosine, and *N*-acetylcysteine display promising results. Because the results of randomized clinical trials have been reported using varied endpoints and outcome measures, direct comparisons between different pharmacotherapies cannot easily be evaluated. Additional, high-quality, randomized, double-blind, placebo-controlled trials with long-term follow-up, using validated sustained abstinence measures, are needed in order to find more effective smoking cessation aids.

Introduction

Tobacco use disorder is a chronic illness and a considerable public health challenge [1]. With its high comorbidity rate, tobacco is a major cause of years of life lost or years lived with disability [2]. It is considered the foremost preventable cause of death in developed countries and yet is responsible for more than 5 million deaths per year [3]. Tobacco smoke also affects passive smokers who will suffer its harmful effects [3]. Costing in the order of billions of dollars annually, smoking cessation constitutes not only a crucial medical need but also a pressing economic need [1].

Since the development of nicotine replacement therapy (NRT) in 1978, pharmacotherapy choices have expanded [3]. In addition to NRT, bupropion and varenicline are approved by the United States Food and Drug Administration (FDA) as first-line treatment options, whereas clonidine and nortriptyline are second-line treatments that are used when first-line treatments fail or are contraindicated, or by patient preference [1]. Despite an increase in available treatment options, current approaches for tobacco cessation have limited utility. Indeed, whereas nearly 70% of smokers want to quit, less than 25% of them will remain abstinent after one year of treatment, and a mere 4-7% will successfully quit permanently [4]. Limited treatment options, low overall treatment efficacy, adverse effects, patient concerns about sustained consumption of nicotine products or weight gain after cessation, low adherence, psychological dependence, and high cost in some countries are explanations for these low cessation rates [5].

Encouraged by these needs, alternative treatment agents are being investigated. Agents such as monoamine oxidase inhibitors (MAOIs); psychostimulants; nicotinic acetylcholinergic receptor (nAChR) antagonists; combination camphor, eucalyptus oil, menthyl valerate, and quinine; and opioid antagonists have shown little to no benefits versus placebo, whereas some other drugs such as *N*-acetylcysteine (NAC) appear promising.

The aim of this article is to provide a narrative review of the development and current status of smoking cessation pharmacotherapies, with a particular emphasis on the most promising novel agents currently under investigation. For this reason, first-line, evidence-based treatments are only briefly summarized, and readers are encouraged to refer to the reviews cited.

Literature Search

A search of Cochrane Database of Systematic Reviews and the PubMed, OVID, and ClinicalTrials.gov databases (2 August to 1 September 2017) was undertaken for articles on smoking cessation pharmacotherapies, applying no language restrictions. The search was conducted using the following terms: “smoking cessation” or “nicotine dependence” or relevant individual drug names and “pharmacotherapy”. Additional related publications were identified using the references of the articles identified.

We found that the approaches used to report on randomized clinical trials outcomes varied greatly [6]. The lack of standard criteria may hinder understanding and comparing those results. The Russell Standard[6] was followed to attempt to unify the inclusion criteria in this review, which required the following: (1) follow-up for 6 months or 12 months from the target quit date or the end of a predefined “grace period”; (2) self-report of smoking abstinence over the whole follow-up period allowing up to five cigarettes in total; (3) biochemical verification of abstinence at least at the 6-month or 12-month follow-up point; (4) use of an “intention-to-treat” approach in which data from all randomized smokers are included in the analysis unless they have died or moved to an untraceable address (participants who are included in the analysis are counted as smokers if their smoking status at the final follow-up cannot be determined); (5) following up “protocol violators” and use their true smoking status in the analysis; and (6) collecting follow-up data blind to smokers’ allocation to trial group. However, studies that did not meet the Russell Standard, such as early phase I/II or preclinical studies, are exceptionally cited in some cases in order to demonstrate lack of evidence, need for more research, or in the case of drugs in early developmental stages.

Evidence-Based Treatments

First-Line Treatments

Nicotine Replacement Therapy

Since the creation of a chewing gum formulation in 1978, the NRT market has continued to evolve, developing patches, oral and nasal sprays, inhalers, and lozenges [3]. The use of NRT is based on the rationale that substituting cigarettes with controlled doses of nicotine would prevent exposure to the harmful substances found in cigarettes [3]. These doses should be ample enough to avoid the appearance of nicotine withdrawal syndrome [3] and reduce the reinforcing effects of smoking [7] while not high enough to create dependency [3]. However, as blood and brain nicotine concentrations are reached more gradually compared to inhalation (e.g., smoking a cigarette), NRT only partially avoids withdrawal symptoms [4].

Given that NRT was the first approved treatment for nicotine dependence, numerous studies and reviews have accumulated in the literature [8, 9]. Robust evidence suggests that NRT products are effective treatments for quitting smoking. As such, it is not surprising that a systematic review including 150 trials, with over 50,000 participants, comparing any type of NRT versus placebo or non-NRT control group, reported that all NRT formulations consistently improved cessation rates. Also, the use of patch therapy for 8 weeks was as effective as longer courses [10]. Notably, NRT has been shown to be effective independent of additional counseling [10].

Bupropion Sustained-Release

Bupropion is a dopamine and norepinephrine reuptake inhibitor, which may also act as a nicotine receptor antagonist, and was initially approved for the treatment of major depressive disorder [4]. During its use as an antidepressant in 1989, it was observed that patients treated with bupropion also incidentally quit smoking; some years later this led to bupropion becoming the first nonnicotinic drug to be approved by the FDA for smoking cessation [11].

Since then, a number of randomized control trials have been conducted, and evidence for the utility of bupropion in promoting smoking cessation is reasonably compelling [12, 13]. Bupropion has been shown to increase cessation rates over placebo at long-term follow-up [14], independent of its antidepressant effects [14]. A recent meta-analysis did not detect a significant difference between bupropion and NRT [15]. Hence, bupropion may be appropriate for patients interested in reducing smoking who dislike or who have failed NRT [16]. Furthermore, there is some evidence to suggest bupropion is associated with shorter periods between cessation attempts and may increase short-term abstinence rates [17].

Varenicline

Varenicline is a partial agonist of nAChRs with strongest affinity for $\alpha_4\beta_2$ receptors [18]. Varenicline is also a slightly less potent full agonist at α_7 and $\alpha_3\beta_4$ nAChRs and is a potent full agonist at 5-HT₃ (serotonin type 3) receptors [18]. Although varenicline is more potent at the α_7 and $\alpha_3\beta_4$ nAChRs and has stronger affinity at $\alpha_4\beta_2$, it is less selective for the latter than nicotine [18]. The drug was approved by the FDA in 2006 as a treatment for smoking cessation. Numerous studies have tested varenicline versus placebo [19], bupropion [20], and NRT [21] in a range of patients, including those with a diagnosis of chronic obstructive pulmonary disease [22] as well as those diagnosed with psychiatric conditions [23, 24]

Two separate meta-analyses [25][2] have shown benefit of varenicline for efficacy to quit smoking at a dosage of 2 mg/day, taken during a 12-week treatment, compared with treatment with placebo or bupropion. A previous version of one of the meta-analyses [2], with a sample size greater than 6000 participants, refuted the postmarketing alert that emerged in 2008 about its possible negative effects on mood and the induction of self-injurious and suicidal behaviors [15, 26]. It did not show an increased risk of adverse effects over placebo (relative risk [RR] 1.06, 95% confidence interval [CI] 0.72–1.55), including neuropsychiatric effects (RR 0.53, 95% CI 0.17–1.67).

Second-Line Treatments

Nortriptyline

Nortriptyline is a tricyclic antidepressant that increases norepinephrine levels, inhibiting noradrenergic reuptake and decreasing neuronal firing in the locus coeruleus. Nortriptyline's mechanism of action in promoting smoking cessation is unclear, but putative mechanisms may involve mimicking the noradrenergic actions of nicotine and/or nicotine receptor antagonism [27].

A meta-analysis conducted by Hughes et al that pooled trials using nortriptyline as the only pharmacotherapy showed a significant benefit of nortriptyline over placebo (odds ratio [OR] 2.03, 95% CI 1.48–2.78 [6 trials]) but a nonsignificant benefit over bupropion (OR 1.30, 95% CI 0.93–1.82 [4 trials]) [14]. Additionally, nortriptyline did not show significant changes in the cessation rate as an NRT adjuvant (OR 1.21, 95% CI 0.94–1.55 [4 trials]).

Of note, several studies chose to exclude subjects with major depressive disorder, suggesting that the effects on smoking cessation are not related to the antidepressant properties of nortriptyline [28, 29].

Clonidine

Clonidine is a selective α -adrenergic receptor agonist, historically prescribed as an antihypertensive agent [4]. However, due to its central nervous system effects, it has been used off-label to treat other medical conditions such as insomnia and attention-deficit-hyperactivity disorder as a conjunctive treatment [30]. It is believed that clonidine might reduce some withdrawal symptoms such as anxiety or restlessness [4], but its role in smoking cessation is still unclear.

A meta-analysis conducted by Gourlay that included six randomized, placebo-controlled, long-term follow-up trials evaluating clonidine versus placebo concluded that clonidine may have a small benefit as a smoking cessation aid (RR 1.63, 95% CI 1.22-2.18) [30]. The same authors, however, pointed out that there was no significant evidence to confirm this hypothesis, since the results of only one of the included trials reached statistical significance. In a further analysis that included all 15 available randomized placebo-controlled studies, the pooled RR was 1.31 (95% CI 1.14-1.51).

Summary

There is robust evidence supporting the use of NRT, bupropion, and varenicline as first-line treatments for smoking cessation. Determining initial suitability depends on patient preference, consideration of the risks of adverse events, and comorbid medical conditions [14]. Nortriptyline and clonidine have shown positive effects on smoking cessation treatments over placebo but not over first-line treatments. Thus, both are considered effective second-line treatments. Notably, in the case of bupropion and nortriptyline, the current consensus is that their effects on smoking cessation are unrelated to their antidepressant activity.

Treatments Shown Not to Be Effective

Selective Serotonin Reuptake Inhibitors

One might expect that antidepressants could improve smoking cessation rates, either through their effect on anxious and depressive symptoms during smoking cessation, or via their purported

action on neural pathways of addiction [3]. A meta-analysis found that none of the seven long-term follow-up, double-blind, randomized clinical trials performed to date supported this hypothesis [14]. Neither sertraline, fluoxetine, or paroxetine exhibited benefits over placebo (RR 0.93, 95% CI 0.71-1.22 [1594 patients]), and nor did fluoxetine when used as an adjunctive treatment with NRT (RR 0.70, 95% CI 0.64-1.82 [466 patients]). These findings suggest that, unlike modulation of dopamine or norepinephrine, direct modulation of serotonin systems may not play a significant role in smoking cessation [14]. Table 1 summarizes studies evaluating antidepressants for smoking cessation.

A later double-blind, placebo-controlled trial evaluated the efficacy of the combination of sertraline and bupirone plus cognitive-behavioral treatment versus cognitive-behavioral treatment alone to promote tobacco abstinence [31]. Although the rate of continuous abstinence at the 26th week of follow-up was 43.5% in the active treatment group and 17.3% in the control group ($p=0.01$), and the OR for continuous abstinence for the active treatment group was 4.74 (95% CI 1.50–14.55), the trial did have methodologic limitations, including the absence of any biochemical validation of abstinence.

Anxiolytics

Studies investigating the use of anxiolytics for promoting smoking cessation are typically substantiated on the basis on two observations. First, smoking may be used as a form of self-medication for anxiety; and second, cessation of smoking can induce reductions in mesolimbic dopamine concentrations, which consequently provokes withdrawal symptoms such as restlessness, insomnia, or anxiety [32]. In both cases, it is hypothesised that anxiolytic compounds may provide some therapeutic relief, potentially making them a useful smoking cessation aid [3]. Interestingly, a meta-analysis found no significant difference between diazepam (a benzodiazepine) and placebo at long-term follow up (RR 1.00, 95% CI 0.56-1.80) [32]. Benzodiazepines are currently contraindicated for smoking cessation due to their high potential abuse risk [32]. Table 2 summarizes studies evaluating anxiolytics for smoking cessation.

Bupirone, a nonbenzodiazepine anxiolytic without sedative properties and with a low tolerance and dependence risk, was also tested due to its more favorable safety profile [32]. A Cochrane meta-analysis found no benefit of bupirone over placebo (RR 0.76, 95% CI 0.42-1.37); however, the obtained confidence intervals do not rule out its clinical utility [32]. Although busipirone

seemed to show some benefits on cessation rates at 12 months after the end of group therapy in a study conducted by Cinciripini, these results could not be replicated (Table 2) [32].

A study evaluating meprobamate versus placebo was conducted by Schwartz [33]. The results in the placebo arm on reduction of >85% from smoking at follow-up were better than those in the treatment arm. The authors of this study attributed these outcomes to adverse effects associated with meprobamate use, including alcohol sensitivity and somnolence (Table 2).

Monoamine Oxidase Inhibitors

Tobacco smoke contains inhibitors of monoamine oxidase, which can potentiate its addictive properties by acting synergistically with nicotine [3]. Given this, several studies were conducted investigating the use of MAOIs (e.g., moclobemide, selegiline, lazabemide, and sembragiline) for tobacco cessation. Although in theory, these compounds seemed promising, the outcomes of the trials were collectively disappointing [27]. Table 3 summarizes studies evaluating MAOIs for smoking cessation. A Cochrane meta-analysis, which included a single long-term placebo-controlled trial testing moclobemide for smoking cessation and five trials evaluating selegiline, reported no benefit of their use over placebo [14]. Moclobemide use was associated with few adverse effects; however, insomnia was most common, being reported in 36% of subjects receiving the drug.

Although trials initially indicated that selegiline may reduce the number of smoked cigarettes and increase the duration of abstinence, a review concluded that there is not enough evidence to assert that selegiline had indeed affected long-term abstinence (RR 1.45, 95% CI 0.81-2.61) [34]. More recently, three different studies found no benefits of selegiline over placebo for smoking cessation [35-37], even when selegiline was combined with a nicotine transdermal patch [95]. Notably, another trial evaluating selegiline administered in combination with NRT and was terminated early because of its lack of efficacy (ClinicalTrials.gov identifier NTC00390923). Sembragiline, an MAOI prescribed for Alzheimer's disease, was not superior to placebo in abstinence rates in an 8-week, placebo-controlled study; the manufacturer has discontinued its development for this use [14].

Psychostimulants

Modafinil, a psychostimulant with wakefulness-promoting and neuroprotective properties, is indicated for excessive somnolence associated with conditions such as narcolepsy, obstructive sleep apnea, and shift work sleep disorder [3]. Modafinil is suggested as a potentially useful treatment for cocaine dependence [3]. In contrast, the trials conducted for smoking cessation yielded detrimental outcomes and were discontinued [3]. A randomized, double-blind, controlled trial comprising 150 participants and comparing modafinil 100 mg twice daily for 8 weeks versus placebo found that the daily smoking rate was in fact 44% higher in the treatment arm when compared to the placebo arm [38]. As such, given its limited effectiveness, in addition to its cardiovascular adverse effects, modafinil is an unlikely candidate for further evaluation for smoking cessation.

Other Nicotinic Acetylcholine Receptor Agonists and Antagonists

Lobeline is an alkaloid and an nAChR agonist, found in a variety of plants, and was commonly used in the past as a nicotine substitute in smoking cessation therapies [5]. In his review, Stead underscored the methodologic limitations of the studies performed with lobeline, highlighting a deficit in the use of adequate controls, long-term follow-up, or assessment of outcomes other than complete abstinence, and expressing doubts about an appropriate randomization method [39]. Recently, Glover conducted a multicenter phase III study of sublingual lobeline versus placebo, which did not show significant differences in abstinence rates at 6 weeks, presenting a high dropout rate [40].

Mecamylamine, originally marketed as an antihypertensive agent, is a noncompetitive nicotine antagonist [4]. It acts as an autonomic ganglionic blocker within the peripheral nervous system, which may be responsible for its adverse effects [3]. The use of mecamylamine in smoking cessation research is based on its potential to reduce sensitivity to the reinforcing effects of nicotine, and, thus, the pleasure associated with its consumption [4]. Confounding initial hypotheses, studies have shown that low mecamylamine doses may actually increase tobacco consumption [4]. This might be explained by a compensatory response to the reduction of smoking satisfaction. In contrast, higher doses of mecamylamine may be more effective but can induce unwanted side effects such as constipation, headache, blurred vision, urinary retention, or orthostatic hypotension [4].

It was proposed that the coadministration of mecamylamine and nicotine prior to the cessation attempt could decrease smoking rates [41]. A suspected mechanism of action for this assertion is that combination therapy occupies more nicotinic receptors than either agent administered separately, effectively blocking the pleasurable effect of cigarettes [41]. It is also assumed that combination therapy improves tolerance to both treatments, since they can mutually compensate their adverse effects (Table 4). Of note, mecamylamine has now been withdrawn from the market because of declining sales, whereas lobeline was banned by the FDA, and its manufacturers discontinued its development [4].

Quinine-Methyl Valerate-Camphor-Eucalyptus Oil

Nicobrevin (Inter-Brevipharma GmbH, Oberursel, Germany) is a patented product, composed of quinine (which putatively reduces cravings), methyl valerate (with supposed sedative properties), as well as camphor and eucalyptus oil (decongestants) [42]. None of these compounds, however, have been tested in isolation to determine whether they have any effect on smoking cessation [42]. Although two short-term follow-up trials show favorable results of Nicobrevin over placebo or other smoking cessation aids, both of them have important methodologic limitations [42]. One did not ask the participants to try to quit, the primary outcome was not continued abstinence at long-term follow-up, and measured levels of blood carbon monoxide were not related to smoking status [43]. The other one tested a variety of products on the same trial, making it impossible to analyze the results separately [44]. The license was withdrawn in numerous countries [3] and more research is unlikely to be conducted.

Opioid Antagonists

Nicotine increases the activity of the endogenous opioid system within the mesolimbic circuit, which plays an important role in tobacco dependence [3]. The potential benefit of opioid antagonists is attributed to their possible mitigation of the reward effect obtained through smoking cigarettes [5].

Studies available to date show that the opioid antagonist, naltrexone, does not promote smoking cessation (Table 5) [45]. A Cochrane meta-analysis, which included 8 studies and 1213 smokers, reported no significant benefits on continuous abstinence rates for naltrexone over placebo (RR 1.00, 95% CI 0.66-1.51) or when naltrexone was used as an adjunct to NRT (RR 0.95, 95% CI 0.70-1.30) [45]. Moreover, no clear effects of naltrexone on craving, withdrawal symptoms, or

smoking reduction were found. A recently published trial, conducted by Mooney and colleagues, failed to find statistically significant differences in abstinence rates between naltrexone plus bupropion over bupropion plus placebo at 6-month follow-up (27.9% vs. 15.0%, $p=0.09$) [46]. Another study conducted by Fridberg et al. found that naltrexone significantly improved 12-week smoking abstinence rates and decreased smoking urge and alcohol use among heavy-drinking smokers but not moderate-to-light or nondrinking smokers [47]. Mediation analyses in heavy-drinking smokers revealed that naltrexone's effect on smoking urge during the first 4 weeks of treatment mediated its effect on quit rates.

These results, in addition to concerns regarding adverse effects and possible dependence risk, make recommendation of naltrexone as a treatment for smoking cessation unlikely, either as monotherapy or in combination with nicotine (Table 5) [45].

Selective Cannabinoid Type 1 Receptor Inverse Agonists

The cannabinoid type 1 receptor inverse agonists, rimonabant and taranabant, were initially developed as weight loss drugs due to their anorexigenic properties [3]. These appetite regulating compounds may protect against significant postsmoking cessation weight gain [4]. We identified only one trial evaluating taranabant for smoking cessation, which lasted 8 weeks, that assessed prevalence point abstinence for weeks 5-8 as the primary outcome and found no benefit over placebo (OR 1.2, 90% CI 0.6-2.5, $p=0.678$) [48]. Taranabant, as well as rimonabant, were withdrawn from the European market following the identification of severe psychiatric adverse effects, suicidal ideation, and consummate suicide (Table 6) [49]. As a result, these drugs were not approved by the FDA for sale in the United States [4].

Silver Acetate

Similar to use of the disulfiram reaction for alcohol cessation, silver acetate generates an unpleasant metallic taste on contact with the tobacco smoke, in theory making the experience of smoking also unpleasant [4]. Although there were no significant differences observed when compared against placebo in cessation rates, silver acetate may have some short-term efficacy, particularly in lighter smokers [50]. However, given that other smoking cessation interventions produce effects that are comparable to or larger than this, this possible small effect of silver acetate is unlikely to have much clinical relevance (Table 7) [50]. It should also be noted that higher doses of silver acetate may cause argyria [4].

Supplements

As smokers are more likely than nonsmokers to have symptoms of depression, supplements with putative antidepressant properties have been tested [14]. A Cochrane meta-analysis conducted by Hughes concluded that neither the two trials conducted with St. John's Wort versus placebo (RR 0.81, 95% CI 0.26-2.53) nor the one with S-adenosyl-L-methionine (SAME) had significant effects on quit rates or withdrawal symptoms (Table 7) [14].

Other Tricyclic Antidepressants

The only trial with doxepin, to our knowledge, was conducted by Edwards in 1989 [5]. It had a small sample size (19 subjects), and cessation rate at 9 weeks was greater in the treatment arm compared to the placebo arm ($p < 0.02$) [5]. However, one-week postcessation abstinence rates did not show a statistically significant difference. At present, there are no long-term or adequately powered studies that justify its recommendation [5]. Additionally, no statistically significant differences were found in a study with imipramine conducted by Jacobs [14]. Thus, since no long-term studies have been performed with imipramine, recommendation of the drug as an aid for smoking cessation is not justified [14].

5-Hydroxytryptamine₃ Antagonists

After preclinical studies indicated that 5-HT₃ antagonists may reduce the reinforcing effects of several psychoactive drugs, two clinical studies evaluating ondansetron were conducted. Neither of these studies reported any benefit of ondansetron on smoking behavior, withdrawal symptoms, or craving [51, 52].

Agonists of α -Type Peroxisome Proliferator-Activated Receptors

Drugs that activate agonists of α -type peroxisome proliferator-activated receptors (PPAR α) can modulate nicotinic receptors and block nicotine-induced dopamine release [53]. Preclinical data have recently led to the first trial testing the potential efficacy of fenofibrate versus placebo for smoking cessation [54]. Using a crossover design, each of 38 subjects took fenofibrate 160 mg/day for 2 weeks followed by placebo for the other 2 weeks, or vice versa, and smoking cessation was biochemically validated (expired carbon monoxide level <5 parts per million [ppm]). No significant differences between fenofibrate versus placebo were found for number of days quit (mean $\pm$ SEM 1.8 ± 0.3 vs 1.9 ± 0.3 , respectively).

Summary

The negative results of selective serotonin reuptake inhibitor trials suggest that, unlike the modulation of dopamine or norepinephrine, direct modulation of serotonin systems may not play a significant role in smoking cessation. Anxiolytic trials have led to the contraindication of benzodiazepines due to their high potential abuse risk and to the lack of a recommendation for buspirone and meprobamate due to their lack of efficacy. Trials evaluating moclobemide, selegiline, sembragiline, lobeline, naltrexone, silver acetate, St. John's Wort, SAME, doxepin, ondansetron, and fenofibrate have failed to find clear benefits over placebo. In the case of modafinil, trials were discontinued after yielding detrimental outcomes, whereby tobacco consumption was elevated in the treatment arm compared to the placebo arm. Other compounds were withdrawn due to their limited evidence (Nicobrevin) and severe adverse effects (taranabant and rimonabant).

Emerging Treatments

Acetylcholinesterase Inhibitors

Translational studies trialing acetylcholinesterase inhibitors (AChEIs) have yielded favorable results. For example, Ashare and colleagues recently reported results that were consistent with previous studies, suggesting reductions in nicotine reinforcement through cholinergic augmentation [55]. Their most recent trial was designed to determine the effects of repeated administration of combination galantamine-donepezil on voluntary nicotine-taking in rats, as well as on smoking behavior in human smokers [55]. In humans, compared with placebo, repeated galantamine treatment reduced smoking behavior, as well as smoking satisfaction and reward, and was not associated with tolerance and/or significant adverse effects.

Trials with other AChEIs have also been conducted; however, in these studies complete smoking cessation was not the primary outcome. A 12-week, placebo-controlled trial randomized 26 alcohol-dependent smokers to receive rivastigmine 6 mg/day or placebo [56]. The rivastigmine group showed decreases in the number of cigarettes smoked per day, exhaled carbon monoxide level, and tobacco craving, whereas the control group did not exhibit any significant changes. These changes, however, only lasted while the drug was being taken. None of the patients developed an alcohol relapse or an increase in alcohol craving.

These data, while preliminary, encourage further investigation. Nevertheless, as both were pilot trials conducted with small sample sizes, their results should be interpreted with caution.

Agents Affecting γ -Aminobutyric Acid Receptors

Nicotine stimulates the release of a number of neurotransmitters, including γ -aminobutyric acid (GABA). Thus, it has been proposed that medications that affect GABA neurotransmission may be useful as pharmacologic treatments for tobacco addiction [3].

Baclofen is a muscle relaxant that acts to alter GABAergic signaling, predominantly at a medullary level [4]. We identified only one trial assessing smoking cessation as the primary outcome. This phase II trial was finalized with a 6-month follow-up that compared baclofen 30 or 60 mg/day for 8 weeks that included a 2-week induction and 2-week dose reduction period versus placebo (ClinicalTrials.gov identifier NCT01821560). However, although the study has been completed, to our knowledge, results remain unpublished.

Topiramate has intricate mechanisms of action, involving GABA_A receptor activation, glutamate antagonism, and carbonic anhydrase and sodium channel inhibition [4, 57]. The drug is approved by the FDA as both an anticonvulsant and as a prophylactic treatment for migraine [57]. Two studies conducted by Anthenelli and Oncken comparing topiramate 200 mg/day versus placebo for 11 and 12 weeks, respectively, reported no significant differences between the topiramate and placebo arms [57, 58]. Logistic regression analysis in the Anthenelli and colleagues' trial, however, reported significant gender-specific differences [58]. Men treated with topiramate were more likely to quit smoking than women treated with topiramate (37.5% vs 3.7%; OR 15.6; $p=0.016$), but that difference became nonsignificant when compared to placebo-treated men (37.5% vs 13.6%; OR 3.8; $p=0.098$). Men taking topiramate also reported significantly lower tobacco withdrawal scores than both women taking topiramate and men taking placebo. Nonetheless, it is important to note that these trials all had small sample sizes, were open-label design, and had a short follow-up.

Studies investigating the efficacy of topiramate treatment in alcohol-dependent smokers have yielded conflicting results. Whereas topiramate initially showed benefits over placebo [59, 60], recent work published by Anthenelli refutes that finding in a phase II, randomized, sequential, parallel-group, controlled study, with 129 participants receiving topiramate (titrated up to 200

mg/day) or placebo, with a 24-week nontreatment follow-up period [61]. Smoking cessation rates were similar in both the topiramate-treated group (7.3%) and placebo group (10.6%; OR 1.60; 95% CI 0.4-6.5; $p=0.51$). Both arms showed a similar relapse rate to that of drinking or drug use (31.8% for the topiramate group vs 27.3% for the placebo group, $p=0.58$). Results of a longitudinal logistic regression analysis examining time to any alcohol relapse revealed no medication effect (ClinicalTrials.gov identifier NCT00802412). The recently published study conducted by Isgro and colleagues was the first to examine smoking differences in types A and B alcohol-dependent individuals [62]. Type B alcoholics demonstrated suppressed levels of smoking in response to topiramate treatment compared with placebo but only during the nontreatment follow-up phase. This effect was mediated, in part, through intention to smoke and craving to smoke to relieve negative affect.

Gabapentin is an anticonvulsant whose specific mechanisms of action remain uncertain [63]. It has been suggested that gabapentin may affect the neuronal L-amino acid system and is currently approved to treat epilepsy and neuropathic pain [63]. A trial conducted by White compared gabapentin (titrated up to 1600 mg/day) and bupropion 150 mg twice/daily for 6 weeks [64]. Although prolonged abstinence with bupropion was 26.3% versus 5.9% with gabapentin, these findings did not reach statistical significance ($p=0.1821$), and the study was underpowered. In a later study, Sood compared gabapentin titrated up to 600 mg 3 times daily versus placebo over 8 weeks [63]. They found a prolonged smoking abstinence rate of 24% (95% CI 13–38%) at 6 months among participants treated with gabapentin as well as a significant reduction in the number of cigarettes smoked per day at the 6-month follow-up compared to baseline. On the other hand, in a subsequent study conducted by the same author, gabapentin-treated participants exhibited lower abstinence rates than placebo-treated participants; however, this difference was not significant [65].

Finally, it is worth mentioning that the GABA aminotransferase inhibitor vigabatrin was found to have favorable effects on craving and reinforcement in preclinical experiments using animal models of smoking. To our knowledge, however, no clinical trials have evaluated the efficacy of vigabatrin in treating smoking cessation in humans [4].

N-Methyl-D-Aspartate Receptor Modulators

There is some evidence suggesting that glutamatergic transmission mediates the primary reinforcing effects of nicotine and intervenes in nicotine reward and symptoms of withdrawal in preclinical models [66]. This justifies current research into agents modulating *N*-methyl-D-aspartate (NMDA) receptors such as memantine, cycloserine, and *N*-acetylcysteine.

Cycloserine

Cycloserine is a broad-spectrum antibiotic with good CNS penetrance being investigated for its potential role in enhancing cue exposure therapy in the treatment of addiction [4]. Two small trials evaluating D-cycloserine did not reduce smoking behavior in smokers or cocaine-dependent smokers, independent of other factors [67]. A phase I trial investigating D-cycloserine as an augmentation treatment of smoking cessation in individuals with panic attacks is currently in its recruitment phase (ClinicalTrials.gov identifier NCT01944423). Participants will be randomized to D-cycloserine (one pill one hour prior to sessions 3, 4, and 5) or placebo. Both arms will also receive 7 weeks of panic and smoking reduction treatment and NRT beginning on the quit date (week 5) using the 3-step tapering Nicoderm process (21 mg, 14 mg, and 7 mg).

Memantine

Memantine is a noncompetitive, selective NMDA receptor antagonist approved for dementia [3]. A short-term follow-up study conducted by Thuerauf et al. demonstrated that memantine does not influence cigarette consumption, craving, or the hedonic estimation of nicotine under the condition of instructed smoking reduction [68].

N-Acetylcysteine

N-Acetylcysteine (NAC) is an antioxidant precursor of glutathione and cysteine, an NMDA receptor modulator, and also has some antiinflammatory effects [66]. Predicated on its theoretical impact on cysteine glutamate exchange [69], several studies have revealed the potential utility of NAC in the treatment of nicotine addiction. For example, Froleinger conducted a double-blind trial in which 16 participants were randomized to NAC 2400 mg/day or placebo for 3.5 days [70]. Mood, craving, and expired-air carbon monoxide level were measured each day of the study, and on day 4, a functional magnetic resonance imaging scan was conducted on each participant. The treatment arm subjects reported higher maintained abstinence rates, positive affect, and less craving. Moreover, they exhibited stronger resting-state functional connectivity between ventral striatal nodes, medial prefrontal cortex and precuneus, and the cerebellum.

A 12-week, double-blind trial randomizing 34 participants to NAC 3 g/day or placebo was conducted by Prado [66]. Both arms received smoking-focused group behavioral therapy. The NAC arm showed a significantly lower number of daily smoked cigarettes and higher quitting rates, defined by expired-air carbon monoxide level <6 ppm (47.1% for the NAC arm vs 21.4% for the placebo arm). NAC treatment significantly reduced the Hamilton Depression Rating Scale score in patients with tobacco use disorder.

The first trial combining NAC with another active treatment was conducted by McClure [71]. This was an open-label pilot trial with a sample size of 19 patients comparing NAC 1200 mg twice daily plus varenicline (1 mg twice daily, following titration) for 4 weeks versus placebo. Participants received weekly assessments concerning adverse events, smoking, craving, and withdrawal. Exploratory analyses showed reductions in cigarettes smoked per day, although point prevalence abstinence at the end of the study was low [71]. These data encourage future research on combined NAC and varenicline treatment for smoking cessation.

Cytisine

Cytisine is a partial agonist that binds with high affinity to the $\alpha_4\beta_2$ subtype of the nicotinic acetylcholine receptor [4]. The use of cytisine began centuries ago in America, where the compound was consumed for its emetic effects [72]. It was introduced commercially in the 1960s as a smoking cessation aid in Bulgaria, and later, in other Eastern European countries, where cytisine is still available [3]. Although this product has been widely used as treatment, its approval was based on small trials that would not meet current regulatory standards [2].

A meta-analysis by Cahill included two trials and 937 participants [2]. Both trials reported continuous abstinence rates at longest follow-up (24 weeks and 52 weeks), showing that the treatment arm had significant benefits over placebo (pooled RR 3.98; 95% CI 2.01-7.87). However, absolute quit rates were relatively low: 8.4% and 9% for cytisine and 2.4% and 1% for placebo at 24 and 52 weeks, respectively. The authors decided to omit the trial conducted by Scharfenberg in their meta-analysis, as it did not report any biochemically validated abstinence method. The trial conducted by Scharfenberg reported an abstinence rate of 1.91% at 6 months (95% CI 1.53-2.37) and 1.61% (95% CI 1.24-2.08) at 2-year follow-up.

The largest trial to date held with cytisine was performed by Walker in 2014 [73]. It was a randomized, open-label, parallel-group, controlled, noninferiority study with 1360 participants randomized to a course of cytisine or NRT. All participants received low-intensity, telephone-delivered behavioral support through a quitline (smoking cessation service available through a toll-free telephone number). Although this trial was designed as a test of noninferiority, it demonstrated a significant benefit for cytisine over NRT (RR 1.43, 95% CI 1.13-1.80). The primary endpoint finding at one month also favored cytisine (RR 1.30, 95% CI 1.12-1.51). However, the validation measure was self-reported abstinence (not a biochemical measure), and they did not report verified continuous abstinence at 6 months.

Dopamine Enhancers and Receptor Modulators

As mentioned above, the dopaminergic circuits are implicated in the reinforcement effects of nicotine. As such, dopamine enhancers and receptor agonists have been, or are currently being investigated, for smoking cessation [3].

Dopamine-enhancing levodopa-carbidopa treatment was tested in an open-label study of 193 participants, yielding no benefits on smoking quit rates and withdrawal symptoms compared to placebo [74]. Currently, trials with other dopamine agonists (bromocriptine [75]) and antagonists (GSK598809, ClinicalTrials.gov identifiers NTC00437840 and NCT00605241) are being conducted, but the assessed primary outcome is craving or consumption of cigarettes rather than smoking cessation.

New Galenic Formulations of Varenicline

In order to develop more effective forms of varenicline and extend patent life, new formulations such as sustained release and patch are being tested [3]. We identified only two phase I trials assessing sustained-release varenicline's safety, tolerability, and pharmacokinetics, but no results are presently available (ClinicalTrials.gov identifiers NCT00731562 and NCT00527150). A third study, a phase II study, evaluating the safety and efficacy of three doses of a controlled-release formulation of varenicline was withdrawn (ClinicalTrials.gov identifier NCT00741884). Two phase I trials evaluating a transdermal delivery system of varenicline formulation have been completed (ClinicalTrials.gov identifiers NCT01013454 and NCT01234142), with no available results and a patent application lodged (US 20110086086 A1).

New Nicotine Delivery Products

New nicotine delivery products are being developed in an attempt to circumvent the unpleasant taste of conventional NRTs [3]. Some of these delivery products, such as a high-strength patch, fast-dissolving oral strips, mini-lozenges, or a nicotine pouch, are available in some countries, although relatively limited evidence of efficacy is given. Mouth spray, available since 2011, showed increased long-term cessation rates versus placebo, producing superior effects to establish the efficacy of NRT, with 13.8% of subjects abstinent at 12-month follow-up [76]. In contrast, nicotine drinking straws and liquid drops do not seem to be useful because of nicotine's first-pass metabolism and interaction with the pH of the drink [76]. At present, other delivery systems, such as rapid-delivery gum or carbon nanotube delivery systems, are still in the development stage [76].

E-cigarettes were introduced into the market in 2003 [3]. Since then, their usefulness and recommendation for their use have been controversial, and regulation varies from country to country [3]. It is worth mentioning that their clinical efficacy on smoking cessation and long-term safety remains strongly debated [77, 78], although its discussion is outside the scope of this review. The most recent Cochrane meta-analysis concluded that subjects using e-cigarettes were more likely to have abstained from smoking for at least 6 months compared with participants using placebo e-cigarettes (RR 2.29, 95% CI 1.05-4.96; 6-month abstinence rates of 4% for placebo vs 9% for e-cigarettes) [79]. Only one study comparing e-cigarettes to the nicotine patch was included in this meta-analysis, showing no significant difference in 6-month abstinence rates (RR 1.26, 95% CI 0.68-2.34). Nevertheless, the authors expressed their concern about the results due to the small number of trials, low event rates, and wide confidence intervals around the mean.

Nicotine Vaccines

The development of nicotine vaccines is based on the rationale that introduction of anti-nicotine antibodies can reduce the amount of nicotine penetrating the blood-brain barrier by binding with it in the periphery and, thereby, decrease its reinforcing effects [3]. At present, there are four existing conjugate vaccines (NIC002, Niccine, NicVAX, TA-NIC) under development by pharmaceutical companies [3].

A Cochrane review that included four trials and 2642 participants compared nicotine vaccines and placebo [80]. None of the four studies detected a statistically significant difference in 12-month follow-up cessation rates between treatment and placebo arms (RR 1.35, 95% CI 0.82-2.22 for NIC002; RR 1.74, 95% CI 0.73-4.18 for NicVAX). The two phase III NicVAX trials, which is the most developed of all vaccines, reported similar quit rates of approximately 11% in both arms.

Later studies have failed to find any benefit of Niccine nor NicVAX on smoking status. Tonstad and colleagues conducted a randomized, double-blind, parallel-group, 1-year trial comparing Niccine versus placebo [81]. At 1 year, nonrelapse was 43.3% in the Niccine group versus 51.1% in the placebo group (difference -7.9%, 95% CI -20.6 to 4.9). There was no benefit of Niccine on smoking status at 6 or 9 months, exhaled carbon monoxide levels, time to relapse, abstinence, withdrawal symptoms, or smoking reinforcement.

Recently, Hoogstender conducted a phase IIb, multicenter, double-blind, randomized, placebo-controlled trial to assess the efficacy of the nicotine vaccine NicVAX coadministered with varenicline and intensive counseling as an aid in smoking cessation and relapse prevention [82]. No significant difference was noted in abstinence rates between NicVAX and placebo from weeks 9 to 52 (27.7% vs 30.0%; OR 0.89, 95% CI 0.62-1.29) or weeks 37 to 52 (33.8% vs 33.2%; OR 1.03, 95% CI 0.73-1.46).

Summary

Several compounds have recently yielded encouraging results in pilot trials, the most promising of which are perhaps the AChEIs and NAC. Galantamine-donepezil and rivastigmine have been shown to reduce smoking behavior, satisfaction, and reward compared with placebo, as well as NAC, which has been shown to reduce the number of daily smoked cigarettes and increase quitting rates. On the other hand, agents affecting GABA receptors, such as topiramate, showed conflicting results, both, in the general population and alcohol-dependent smoker cohorts. In general population cohorts, some studies found no significant difference over placebo, whereas others reported significant gender-specific differences. A recent trial investigating the efficacy of topiramate treatment in alcohol-dependent smokers reported suppressed levels of smoking in response to topiramate treatment compared with placebo in type B alcoholics but only during the nontreatment follow-up phase. Gabapentin has shown no benefit over bupropion, and results

versus placebo were not statistically significant. Vigabatrin is still in preclinical phases, and no clinical trials have yet evaluated the efficacy of vigabatrin in treating smoking cessation in humans. Cytisine, approved in some countries based on small trials that would not meet current regulatory standards, have shown benefits over placebo in a meta-analysis, and over NRT, although these results have to be interpreted with caution due to the methodologic limitations of the studies. Levodopa-carbidopa, new formulations of varenicline, and nicotine vaccines have not shown any benefits over placebo.

Conclusion

Smoking remains an important public health concern, with significant repercussions on the health of smokers and those who surround them. Although NRT is the dominant pharmacotherapy for smoking cessation, 70-90% of smokers relapse despite treatment. Accordingly, first- and second-line treatments remain insufficient. Numerous treatments have been investigated, some of them unsuccessfully. Although benzodiazepines are contraindicated due to their risk of abuse, other drugs such as Nicobrevin, taranabant, and rimonabant were withdrawn due to their lack of efficacy and severe adverse effects. Moreover, modafinil may actually increase tobacco consumption rather than decrease it. Moclobemide, selegiline, sembragiline, lobeline, naltrexone, silver acetate, St. John's Wort, SAME, doxepin, ondansetron, and fenofibrate have failed to find benefit over placebo. More promising are the results showed by AChEIs and NAC, which may reduce smoking behavior, satisfaction, and reward. Other molecules, such as agents affecting GABA receptors, cytisine, new galenic formulations of varenicline, or new nicotine delivery products, are being investigated with nonconclusive results.

More gold-standard trials (randomized, double-blind, placebo-controlled trials with long-term follow-up and using validated sustained abstinence methods) are needed to identify more effective smoking cessation aids that facilitate sustained abstinence and reduce nicotine reinforcement, craving, and withdrawal symptoms. Furthermore, higher quality studies are required with novel pharmacotherapies, including larger sample sizes and outcomes measured at longer time points (12 months) using biochemical measures to confirm abstinence. Studies recruiting populations with special needs, and evaluations of treatment programs and combination therapies, are also essential to facilitate personalized treatments. Some new drugs such as AChEIs, Cytisine, and NAC show promising results, and new investigations should be encouraged.

Hypotheses for Antidepressant Use for Smoking Cessation	Drug	Study	Study Design	Intervention	Validation	Results
1. Anxiety-depressive symptoms as part of the smoking cessation syndrome 2. Action on the addiction neural pathways	Paroxetine	Killen 2000[83]	Randomized, double-blind, controlled trial (n=224)	Nicotine patch 21 mg/day for 8 weeks + paroxetine 40 mg/day for 9 weeks (including tapering) vs paroxetine 20 mg/day or placebo All participants: 15 min of behavioral counseling at weeks 1 and 4	Expired-air CO < 9 ppm and saliva cotinine <20 ng/ml at each visit	Abstinence at 6 months (7 day PP at 10 and 26 weeks): No statistically significant differences: RR 1.08; 95% CI 0.64 -1.82
	Sertraline	Covey 2002[84]	Randomized, double-blind, controlled trial (n=134) (smokers with a history of MDD)	Sertraline 200 mg/ day for 11 weeks vs. placebo All participants: 9 x 45-min individual counseling sessions	Serum cotinine < 25 ng/ml	Abstinence 6 months after EOT (7 day PP): No statistically significant differences: RR 0.71; 95% CI 0.30-1.64. No moderating effects of single or recurrent major depression, depressed mood at baseline, nicotine dependence level, or gender were observed
	Fluoxetine	Blondal 1999[85]	Randomized, double-blind, controlled trial (n=100)	Fluoxetine 20 mg/day initiated 16 days before TQD + nicotine inhaler for 3 months vs. placebo + nicotine inhaler. Advised to use 6-12 inhalers/day for up to 6 months All participants: 5 x 1-hour group behavior therapy sessions	Expired-air CO < 10 ppm	Abstinence at 1 year (sustained from quit day): not significant at any time point: RR 0.90; 95% CI 0.43- 1.90 Fluoxetine appeared to increase abstinence rates among smokers with high BDI compared to smokers with high BDI who received placebo
		Niaura 2002[86]	Randomized, double-blind, controlled trial (n=989)	Fluoxetine 30 mg vs. fluoxetine 60 mg vs. placebo for 10 weeks, starting 2 weeks before TQD All participants: 9 sessions (60-90 minutes) of individual behavior therapy	Saliva cotinine < 20 ng/mL at each visit	Abstinence at 32 weeks from TQD, multiple PP: no evidence of a significant effect at any time point, alone or as an adjunct to NRT

Author Manuscript		Saules 2004[87]	Randomized, double-blind, controlled trial (n=150)	Fluoxetine 20 or 40 mg/day for 14 weeks + nicotine patch for 10 weeks vs. placebo + nicotine patch with same schedule All participants: 6 sessions of behavior therapy starting 2 weeks before TQD	Expired-air CO < 10 ppm	Abstinence at 12 months: no evidence of a significant effect: RR 0.94; 95% CI 0.41 - 2.18, either for those with or without MDD histories or elevated current depression. Withdrawal symptoms: scores were significantly lower in both fluoxetine groups
		Spring 2007[88]	Randomized controlled trial (n=247)	Fluoxetine 60 mg for 12 weeks vs. placebo All participants: 9 group behavioral counseling sessions over 12 weeks	Expired-air CO < 10 ppm, urine cotinine < 20 ng/ml	Abstinence at 6 months (prolonged from 2 weeks after quit date): fluoxetine initially increased cessation among smokers with a history of depressive disorder. By the end of the study, it impaired cessation regardless of depressive history
		Brown 2013 [89]	Randomized controlled trial (n=216) (smokers with elevated depressive symptoms)	Fluoxetine 20 mg/day for 10 weeks (beginning 2 weeks prior to TQD) vs. fluoxetine 20 mg/day for 16 weeks (beginning 8 weeks prior to TQD) vs. placebo All arms: nicotine patch for 8 weeks starting on TQD (21 mg/day for 4 weeks, 14 mg/day for 2 weeks, 7 mg/day for last 2 weeks) All participants: 5 sessions of brief behavioral therapy (in person and by phone over 4 weeks, 20-30 minutes each)	Salivary cotinine < 10 ng/ml	Continuous abstinence at 12 months: significantly impaired cessation in the group receiving 10 weeks of treatment. No significant effect on the group receiving 16 weeks of treatment: RR 0.61, 95%CI 0.29- 1.27
	Venlafaxine	Cinciripini 2005 [90]	Randomized controlled trial N=147	- Venlafaxine titrated to max of 225 mg/day from 3weeks before QD for 21weeks, including 2weeks tapering vs. placebo + Both arms: 6weeks 22 mg nicotine patch, and 9x 15 min behavioural counselling	CO ≤ 10 ppm and/or saliva cotinine < 15 ng/ul	Abstinence at 12m (PP): no significant differences, but confidence intervals do not exclude a clinically useful effect (RR 1.22, 95% CI 0.64 to 2.32)

Table 1. Summary of Studies Evaluating Antidepressants for Smoking Cessation

Studies were included only if they had long-term follow-up and used validated sustained abstinence measures.

BDI: Beck Depression Inventory score; CI: confidence interval; CO: carbon monoxide; EOT: end of treatment; MDD: major depressive disorder; NRT: nicotine replacement treatment; PP: prevalence point; ppm: parts per million; RR: relative risk; TQD: the quit day;

Author Manuscript

Hypotheses for Anxiolytic Use for Smoking Cessation	Drug	Study	Study Design	Intervention	Validation	Results
1. Anxiety as withdrawal symptom 2. Smoking as self-medication	Diazepam	Hao 1988	No details given (only described as randomized) (n=118)	Diazepam 7.5 mg/day vs clonidine 0.225 mg/day vs placebo for 4 weeks All participants: 3 individual sessions with a psychiatrist	No biochemical measures of smoking were used. Family and coworkers were questioned.	Continuous abstinence at follow-up on average of 4.5 months from EOT: No significant differences: RR 1.00, 95% CI 0.56–1.80; Quit rates approximately 37% in each group, and withdrawal symptom scores were similar in each group
	Buspirone	Hilleman 1994 [91]	Randomized, open-label, parallel-group design (n=208)	Buspirone 15 mg for 7 days then 30 mg for 21 days vs. fixed-dose transdermal nicotine 21- or 22-mg patch vs. tapered dose 21- or 22-mg, 14-mg, 7-mg patch All participants: 12 weekly behavioral modification sessions	Random plasma thiocyanate testing (partial validation)	Abstinence at 24 weeks: No significant differences: RR1.08; 95% CI 0.70-1.65
		Cinciripini 1995 [92]	No details given (n=101)	Buspirone 45 mg/day maximum for 4 weeks PQD, increasing to 60 mg/day maximum after quit for 12 weeks vs placebo All participants: 9 sessions of cognitive behavioral intervention	Salivary cotinine <14 ng/ml	Cessation at 12 months after end of group therapy: Buspirone enhanced the rate of abstinence only in smokers with high levels of anxiety and only for as long as the drug was available. RR 0.74; 95% CI 0.32-1.72 No effect on long-term abstinence or withdrawal symptoms.
		Schneider 1996 [93]	Randomized, double-blind, controlled (n=100)	Buspirone 30 mg/day maximum for 3 weeks PQD, increasing to 60 mg/day maximum for 6 more weeks vs. placebo All participants: 17 presentations on coping and	Expired air ≤ 8 ppm	Abstinence at 12 months with no reported slips: No significant differences: RR 1.15; 95% CI 0.38-3.53 Withdrawal symptoms: No significant differences Adverse effects: only significant difference was for

				relapse prevention skills		lightheadness (higher in buspirone group) Post hoc division into high- and low-anxiety groups: No evidence of differential effect
	Meprobamate	Schwartz 1968 [33]	No details given (n=324)	Meprobamate 400 mg/day in a factorial design trial for 8 weeks vs. placebo, both alone or in combination with group or individual counseling	No biochemical measures of smoking were used	Success was defined by a reduction of >85% from baseline smoking at follow up. Follow-up at end of treatment (8 weeks), 4 months, and 1 year with telephone follow-up of successes at 18 months: Subjects receiving placebo had better results

Table 2. Summary of Studies Evaluating Anxiolytics for Smoking Cessation

Studies were included only if they had long-term follow-up and used validated sustained abstinence measures.

CI: confidence interval; EOT: end of treatment; ppm: parts per million; PQD: prior to the quit day; RR: relative risk.

Hypothesis for MAOI Use for Smoking Cessation	Drug	Study	Study Design	Intervention	Validation	Results
MAOIs Hypothesis: MAOIs of tobacco smoke may enhance addiction together with nicotine	Moclobemide	Berlin 1995 [94]	Randomized, double-blind, parallel-group, controlled trial (n=88)	Moclobemide 400 mg/day for 2 months, then 200 mg/day during the third month vs. placebo	Plasma cotinine $\leq$ 20 ng/ml at all visits. 1-year abstinence based on telephone self-report by 6-	Prolonged abstinence at 12 months: Not superior to placebo: RR 1.57; 95% CI 0.67-3.68 Withdrawal symptoms, Montgomery-Asberg Depression Rating Scale scores, and Hamilton anxiety scores: no significant differences Plasma dihydroxyphenylglycol levels: no changes in the placebo group, but levels decreased in a dose-dependent fashion in the moclobemide arm

Author Manuscript					month quitters	More subjects reported insomnia with moclobemide
	Selegiline	Biberman 2003 [95]	Randomized, double-blind, controlled trial (n=109)	Selegiline 2.5 mg twice/day initiated 1 week before TQD, increasing to 5 mg twice daily for 26 weeks vs. placebo All participants: active nicotine skin patch for the first 8 weeks only + weekly behavioral support visits, then visits every 2 weeks for 12 weeks	Urine nicotine, cotinine, 3-hydroxycotinine at all visits	Continuous abstinence at 52 weeks: trend in favor of the group that received treatment with selegiline and NRT vs NRT alone, but no significant benefits: RR 2.21, 95% CI 0.92-5.32 Selegiline augmentation did reduce the craving at week 4 compared with placebo No significant differences at baseline in Beck Depression Inventory scores between arms. No serious adverse events reported
		George 2003 [96]	Randomized controlled trial (n=40)	Selegiline 5 mg twice daily for 9 weeks (5 mg/day during weeks 1 and 9) vs. placebo All participants: weekly counseling	Expired-air CO ≤ 10 ppm	Abstinence at 6 months (7-day PP): Not superior to placebo: RR 4.00; 95% CI 0.49- 32.72
		Weinberger 2010 [35]	Randomized, double-blind, controlled trial (n=101)	Selegiline 10 mg/day for 9 weeks (5 mg/day during weeks 1 and 9) vs. placebo All participants: brief counseling weekly	Expired-air CO and cotinine	Abstinence at 6 months (7-day PP): no significant differences RR:4.00; 95% CI 0.49- 32.72 Comparable adverse effects between arms
		Kahn 2012 [36]	Randomized, double-blind, parallel-group, controlled trial (n=246)	Selegiline patch 6 mg/24 hrs for 9 weeks vs. placebo patch on same schedule All participants: 9 weekly individual counseling sessions of approximately 10 min each	Expired-air CO ≤ 9 ppm	Abstinence at 6 months, continuous from week 6 onward: Not superior to placebo: RR 1.62; 95% CI 0.65-4.05
		Killen 2010 [37]	Randomized, double-blind controlled trial (n=243)	Selegiline patch 6 mg/24 hrs for 8 weeks vs. placebo All participants: 9 sessions of individual CBT	Expired-air CO ≤ 10 ppm	7-day PP at 12 months: Not superior to placebo: RR 0.97; 95% CI 0.59-1.60 No effect of selegiline patch on craving Adverse event rates were similar in both arms

Table 3. Summary of Studies Evaluating Monoamine Oxidase Inhibitors for Smoking Cessation

Studies were included only if they had long-term follow-up and used validated sustained abstinence measures.

MAOIs: monoamine oxidase inhibitors; CI: confidence interval; CBT: cognitive behavior therapy; CO: carbon monoxide; PP: prevalence point; ppm: parts per million; RR: relative risk; TQD: the quit day.

Author Manuscript

Hypothesis for nAChR Antagonist Use for Smoking Cessation	Drug	Study	Study Design	Intervention	Validation	Results
Given the proven efficacy of varenicline (a partial agonist of nAChR), antagonists may be useful	Mecamylamine	Rose 1994 [97]	Randomized, double-blind (n=48)	2 weeks PQD: nicotine patch 21 mg/24 hours plus mecamylamine 10 mg/day vs. nicotine patch 21 mg/24 hours alone vs. mecamylamine 10 mg/day alone vs. placebo After quit date: Nicotine patch 21 mg/24 hours for 4 weeks, then 7 mg/24 hours for 2 weeks plus mecamylamine 10 mg/day for 3 weeks vs. nicotine patch on same schedule plus placebo All subjects received self-help materials to assist cessation (a minimal behavioral intervention)	Expired-air CO $\leq$ 8 ppm	Continuous abstinence through 7 weeks after cessation: 3 times higher in the mecamylamine groups vs placebo (50% vs. 16.7%, $p = 0.015$). Point abstinence at 7 weeks was 58% for mecamylamine vs. 29% for placebo ($p=0.044$). Continuous abstinence at 12 months: remained higher for mecamylamine versus placebo (37.5% vs. 12.5% at 6 months, $p=0.046$; 37.5% vs. 4.2% at 12 months, $p=0.004$) High rates of constipation reported in mecamylamine groups

		Rose 1998	Randomized, double-blind (n=80)	4 weeks PQD: nicotine patch 21 mg/24 hours plus mecamylamine 2.5-5.0 mg twice/day vs. nicotine patch 21 mg/24 hours alone vs. mecamylamine 2.5-5.0 mg twice/day alone vs. placebo After quit date: all groups received nicotine patch 21 mg/24 hours for 6 weeks, then 7 mg/24 hours for 2 weeks plus mecamylamine 2.5-5.0 mg twice/day for 6 weeks	Expired-air CO $\leq$ 8 ppm	Continuous abstinence at 6 months: no significant differences. After Kaplan-Meier survival analysis, a significant benefit was detected for the two groups receiving mecamylamine prior to cessation compared with the groups not receiving mecamylamine 40% of subjects required a reduction in mecamylamine dose
		Rose 2006	Randomized, partially blinded, 3x2x3 factorial controlled trial (n=96)	Factorial design: 3 (usual brand vs. low tar and nicotine cigarette vs. denicotinized cigarette) x 2 (21-mg nicotine patch vs. placebo patch for 2 weeks PQD) x 3 (0-mg vs. 21-mg vs. 42-mg nicotine patch dose for 4 weeks PQD) After the quit-smoking date, all subjects received mecamylamine 10 mg/day for 4 weeks + NRT (0, 21, or 42 mg/24 hrs) for 4 weeks, then 7 mg/24 hours for 2 weeks	Expired-air CO $\leq$ 8 ppm	Abstinence at 6 months: no statistical significance - Pre-cessation nicotine patch treatment was associated with a significantly higher rate of continuous smoking abstinence at 4 weeks, regardless of cigarette condition

Table 4. Summary of Studies Evaluating Nicotinic Acetylcholinergic Receptor Antagonists for Smoking Cessation

Studies were included only if they had long-term follow-up and used validated sustained abstinence measures.

nAChR: nicotinic acetylcholinergic receptor; NRT: nicotine replacement treatment; PQD: prior to the quit day; ppm: parts per million.

Hypothesis for Opioid Use for Smoking	Drug	Study	Study Design	Intervention	Validation	Results
---------------------------------------	------	-------	--------------	--------------	------------	---------

Cessation						
Opioids may mitigate the reward effect obtained with smoking cigarettes	Naltrexone	Covey 1999 [98]	Randomized double-blind, controlled trial (n=80)	Naltrexone 25 mg/day for at least 3 days PQD, increased to 50–75 mg/day on quit date and continued for 4 weeks vs. placebo All participants: weekly individual behavioral counseling	Plasma cotinine ≤ 15 ng/mL	Continuous abstinence at 3 and 6 months: difference at 6 months was not statistically significant (46.7% for naltrexone vs. 26.3% for placebo; OR 2.5, $p < 0.10$) Stratified analysis: usefulness of naltrexone primarily for female smokers and those with a history of major depression. These effects remained 6 months later. No gender difference was observed among subjects without major depression. No effect of naltrexone on withdrawal symptom scores
		Wong 1999 [99]	Randomized, partially blinded, 2 x 2 factorial, controlled trial (n=100)	Naltrexone 50 mg/day for 12 weeks vs. nicotine patch (21 mg/24 hrs for 8 weeks, then 14 mg/24 hrs for 4 weeks) + placebo pill vs. naltrexone 50 mg/day + nicotine patch (21 mg/24 hrs for 8 weeks, then 14 mg/24 hrs for 4 weeks) for 12 weeks vs. placebo pill for 12 weeks. (No placebo patches were used.) All participants: weekly behavioral counseling	Self-reported at 12 weeks; Expired-air CO ≤ 8 ppm at 6 months	Continuous abstinence to 12 weeks (EOT) and 6 months: nicotine patch produced large increases in quit rates (56% for patch vs. 23% for no patch). Naltrexone 50 mg produced no further improvement. No significant effect of naltrexone on daily cigarette smoking or craving during
		King 2006 [100]	Randomized, double-blind, controlled trial (n=110)	Naltrexone 25 mg/day for 3 days, then 50 mg/day for 2 months + nicotine patch 21 mg/24 hrs for 1 month vs. placebo + nicotine patch 21 mg/24 hrs All participants: 6 individual 45-60 minute behavioral therapy sessions	Expired-air CO ≤ 10 ppm	Continuous abstinence at 8 weeks (EOT) and 24 weeks: no significant differences (RR 1.42, 95% CI 0.71- 2.85) Naltrexone significantly reduced cessation-related weight gain and selectively reduced women's urge to smoke
		O'malley 2006 [101]	Randomized, double-blind, controlled trial (n=385)	Naltrexone 100 mg/day vs. naltrexone 50 mg/day vs. naltrexone 25 mg/day vs. placebo All participants also received NRT patch 21 mg/24 hrs x 6 weeks, initial 45-min counseling session, weekly 15-min counseling sessions for 6 weeks, plus self-help materials including dietary and exercise tips	Expired-air CO < 10 ppm	Prevalence point abstinence at 12 months (and continuous abstinence at 6 weeks and 6 months): no statistically significant difference between naltrexone and placebo (RR 1.15, 95% CI 0.60-2.21). Naltrexone 25 and 50mg/day significantly reduced weight gain during the first month of cessation
		Toll 2010 [102]	Randomized, double-blind, controlled	Naltrexone 25 mg/day for 27 weeks vs. placebo	Expired-air CO	Continuous abstinence at 6 weeks and 6 months: no significant differences between naltrexone and placebo (RR 0.81, 95% CI 0.48- 1.37)

		trial (n=172)			No effect of naltrexone on withdrawal symptom scores
	King 2012 [103]	Randomized, double-blind, controlled trial (n=315)	Naltrexone 50 mg/day for 12 weeks + nicotine patch 21 mg/24 hours for 2 weeks, then 7 mg/24 hours for 2 weeks vs. placebo for 12 weeks + nicotine patch on same schedule	Expired-air CO	Continuous abstinence at 12 weeks (EOT) and 6 and 12 months: No statistically significant difference between naltrexone and placebo on continuous abstinence (RR 0.74, 95% CI 0.47-1.16). Naltrexone increased quit rates, attenuated smoking urge, and reduced weight gain only during treatment. Differences between men and women were found: men showed greater reductions in smoking, women showed greater reductions in weight gain
	Mooney 2016 [46]	Randomized, double-blind, controlled trial (n=121)	Bupropion 300 mg/day + placebo or bupropion 300 mg/day + naltrexone 50 mg/day for 7 weeks	Expired-air CO $\leq$ 8 ppm	After 7 weeks of treatment abstinence: 54.1% for bupropion + naltrexone vs 33.3% for bupropion + placebo (p=0.0210) Abstinence at 6-month follow-up: 27.9% for bupropion + naltrexone vs. 15.0% for bupropion + placebo (p=0.09). Continuous abstinence rates did not significantly differ for bupropion + naltrexone vs bupropion + placebo: 26.2% vs 13.3% (p=0.0740)

Table 5. Summary of Studies Evaluating Opioid Antagonists for Smoking Cessation

Studies were included only if they had long-term follow-up and used validated sustained abstinence measures.

CI: confidence interval; EOT: end of treatment; NRT: nicotine replacement treatment; OR: odds ratio; ppm: parts per million; PQD: prior to quit day; RR: relative risk; TQD: the quit day.

Hypotheses for Use of Selective Cannabinoid Type 1 Receptor Agonists and Sensory	Drug	Study	Study Design	Intervention	Validation	Results

Stimulants for Smoking Cessation						
<p>Selective cannabinoid type 1 receptor agonists:</p> <p>Protection against significant postcessation weight gain and restore the balance of the endocannabinoid system that can be disrupted by long-term use of nicotine</p>	Rimonabant	STRATUS EU and US; 2006 [104]	Randomized, double-blind, parallel-group, controlled trial (n=783)	Rimonabant 5 mg/day vs. rimonabant 20 mg/day vs. placebo for 10 weeks, with a target quit date set for day 15, and follow-up for an additional 40 weeks All participants: brief behavioral counseling at every visit	Expired- air CO <10ppm and cotidine	STRATUS EU: no superiority of rimonabant 20 mg/day over either placebo or rimonabant 5 mg/day at any point of treatment STRATUS US: found benefits for rimonabant 20 mg/day at weeks 2–50 and EOT; 7-day point prevalence abstinence at weeks 8, 10, and 50 (RR 1.35, 95%CI 1.00 - 1.82)
		STRATUS WW; 2005 [104]	Randomized, double-blind, parallel-group, controlled trial (n=5055)	<p>- Phase 1 (Cessation): rimonabant 5 mg/day vs 20 mg/day for 10 weeks with TQD at day 15</p> <p>Quitters were eligible for phase 2 if they had self-reported abstinence for ≥ 7 days and CO ≤ 10 ppm and compliance level of $\geq 80\%$ in last 4 weeks of phase 1</p> <p>Phase 2 (Relapse prevention [n=1661]): quitters in previous rimonabant 5-mg group were re-randomized to rimonabant 5 mg/day or placebo, quitters in rimonabant 20-mg group were re-randomized to rimonabant 5 mg/day, rimonabant 20 mg/day, or placebo. All groups received treatment for a further 42 weeks. Successful abstainers at one year were then followed for a further 52 weeks without treatment</p> <p>Phase 3: follow-up for further 52 weeks without treatment</p>	<p>Phase 1: expired- air CO <10ppm</p> <p>Phase 2: not reported</p>	No consistent evidence for the relative efficacy of the two doses, either for cessation or maintenance 2-year follow-up data not reported
Sensory stimulants:	Ascorbic	Westman 1995	Randomized,	Citric acid inhaler (50% citric acid and 50% lactose)	Expired-air	Continuous abstinence at EOT: 19.5% (95% CI 7.4-31.6%) for

Craving reduction due to some of the sensory aspects of smoking substitution	acid	[105]	double-blind, controlled trial (n=100)	for 10 weeks after TQD, with up to 3 refills per day vs. lactose placebo inhalers All participants on TQD added nicotine patches 21 mg/24 hours for 4 weeks, then 7 mg/24 hours for 2 weeks All subjects received self-help materials	CO $\leq$ 8 ppm	the citric acid group vs. 6.8% (95% CI 0.4-13.2%) for the lactose group ($p=0.05$) Abstinence at 10 weeks: 33.3% (95% CI 14.5-52.1%) for participants receiving strong airway sensations from the inhalers Abstinence at 6 months: no significant difference between treatment groups (0% vs. 5.1 %, $p=0.20$)
--	------	-------	--	---	-----------------	---

Table 6. Summary of Studies Evaluating Selective Cannabinoid Type 1 Receptor Agonists and Sensory Stimulants for Smoking Cessation

Studies were included only if they had long-term follow-up and used validated sustained abstinence measures.

CI: confidence interval; CO: carbon monoxide; EOT: end of treatment; ppm: parts per million; RR: relative risk; TQD: the quit day.

Hypotheses for Use of Aversives and Supplements in Smoking Cessation	Drug	Study	Study Design	Intervention	Validation	Results
Aversives: Disulfiram effect	Silver acetate	Hymowitz 1996 [106]	Randomized, double-blind (n=480)	Silver acetate lozenge 2.5 mg 6 times daily for 3 weeks vs. placebo lozenge Successful quitters were given further lozenges to assist relapse prevention All participants: self-help materials, videos, and follow-up visits	Expired-air CO $\leq$ 10 ppm; urinary cotinine $\leq$ 0.6 ng/ml if follow-up visit missed	Sustained abstinence at 12 months: no significant differences between silver acetate and placebo groups (RR 1.04, 95% CI 0.69-1.57)
		Jensen 1990 [107]	Randomized, open-label,	Silver acetate chewing gum 6 mg vs. nicotine gum 2 mg vs. ordinary chewing gum (placebo)	Expired-air CO $\leq$ 4 ppm	Sustained abstinence at 12 months: no significant differences between silver acetate and placebo groups (RR 0.98, 95% CI

<p>Supplements:</p> <p>Smokers are more likely than nonsmokers to have symptoms of depression</p>	St. John's Wort		controlled (n=496)	All participants: 9 sessions of group support		0.69-1.39) Time to relapse: longer for those in the nicotine chewing gum group Adverse effects generally mild and transient in all groups, and unimportant except for mouth irritation from silver acetate
		Parsons 2009 [108]	Randomized, double-blind, 2x2 factorial, controlled trial (n=143)	St John's wort 300 mg 3 times/day for 14 weeks vs. placebo on same schedule; also randomized to chromium 400 µg/day or placebo All participants: 7 weekly individual behavioral support sessions	Expired-air CO ≤ 10 ppm	Prolonged abstinence at 14 weeks: no significant difference between St John's wort and placebo (OR 0.65; 95% CI 0.22–1.92) Prolonged abstinence at 6 months: no significant difference between St John's wort and placebo (OR 0.49; 95% CI 0.12–2.02)
		Sood 2010 [109]	Randomized, double-blind, controlled trial (n=118)	St John's wort 300 mg 3 times/day for 12 weeks vs. St John's wort 300 mg 3 times/day first week increasing to 600 mg 3 times/day for weeks 2-12 vs. placebo on same schedule All participants: 12 weeks of behavioral intervention	Expired-air CO ≤ 8 ppm	Prolonged abstinence at 24 weeks (2-week grace period following quit date) (7-day PP also reported): no significant differences between St. John's Wort dose groups and placebo St. John's Wort did not attenuate withdrawal symptoms among abstinent subjects High dropout rate (43%)
		S-Adenosyl-l-methionine Sood 2012 [110]	Randomized, double-blind, controlled trial (n=120)	SAMe 1600 mg/day for 8 weeks vs. SAMe 800 mg/day for 8 weeks vs. placebo All participants: Approximately 7 behavioral counseling sessions	Expired-air CO ≤ 8 ppm	Prolonged abstinence at 8 and 24 weeks: no significant differences between SAMe dose groups and placebo. Prolonged abstinence at 6 months: no significant differences between SAMe dose groups and placebo (RR 0.70, 95% CI 0.24–2.07) SAMe did not attenuate withdrawal symptoms among abstinent subjects Rates of gastrointestinal adverse effects were higher with SAMe 1600 mg/day compared with placebo High dropout rate (42.5%)

Table 7. Summary of Studies Evaluating Aversives and Supplements for Smoking Cessation

Studies were included only if they had long-term follow-up and used validated sustained abstinence measures.

CI: confidence interval; CO: carbon monoxide; NRT: nicotine replacement treatment; OR: odds ratio; ppm: parts per million; PP: prevalence point; RR: relative risk; SAME: S-adenosyl-L-methionine; TQD: the quit day.

References:

1. *A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report.* Am J Prev Med, 2008. **35**(2): p. 158-76.
2. Cahill, K., et al., *Nicotine receptor partial agonists for smoking cessation.* Cochrane Database Syst Rev, 2016(5): p. Cd006103.
3. Beard, E., et al., *New Pharmacological Agents to Aid Smoking Cessation and Tobacco Harm Reduction: What Has Been Investigated, and What Is in the Pipeline?* CNS Drugs, 2016. **30**(10): p. 951-83.
4. Elrashidi, M.Y. and J.O. Ebbert, *Emerging drugs for the treatment of tobacco dependence: 2014 update.* Expert Opin Emerg Drugs, 2014. **19**(2): p. 243-60.
5. Benowitz, N.L. and M.W. Peng, *Non-Nicotine Pharmacotherapy for Smoking Cessation.* CNS Drugs, 2000. **13**(4): p. 265-285.
6. West, R., et al., *Outcome criteria in smoking cessation trials: proposal for a common standard.* Addiction, 2005. **100**(3): p. 299-303.
7. Foulds, J., et al., *Advances in pharmacotherapy for tobacco dependence.* Expert Opin Emerg Drugs, 2004. **9**(1): p. 39-53.
8. Barboza, J.L., et al., *An update on the pharmacotherapeutic interventions for smoking cessation.* Expert Opin Pharmacother, 2016. **17**(11): p. 1483-96.
9. Wadgave, U. and L. Nagesh, *Nicotine Replacement Therapy: An Overview.* Int J Health Sci (Qassim), 2016. **10**(3): p. 425-35.
10. Stead, L.F., et al., *Nicotine replacement therapy for smoking cessation.* Cochrane Database Syst Rev, 2012. **11**: p. Cd000146.
11. Ferry, L.H., *Non-nicotine pharmacotherapy for smoking cessation.* Prim Care, 1999. **26**(3): p. 653-69.
12. Jorenby, D., *Clinical efficacy of bupropion in the management of smoking cessation.* Drugs, 2002. **62 Suppl 2**: p. 25-35.
13. Martinez-Raga, J., et al., *Treatment of nicotine dependence with bupropion SR: review of its efficacy, safety and pharmacological profile.* Addict Biol, 2003. **8**(1): p. 13-21.

14. Hughes, J.R., et al., *Antidepressants for smoking cessation*. Cochrane Database Syst Rev, 2014(1): p. Cd000031.
15. Cahill, K., et al., *Pharmacological interventions for smoking cessation: an overview and network meta-analysis*. Cochrane Database Syst Rev, 2013(5): p. Cd009329.
16. Ahluwalia, J.S., et al., *Sustained-release bupropion for smoking cessation in African Americans: a randomized controlled trial*. Jama, 2002. **288**(4): p. 468-74.
17. Hatsukami, D.K., et al., *Effects of sustained-release bupropion among persons interested in reducing but not quitting smoking*. Am J Med, 2004. **116**(3): p. 151-7.
18. de Moura, F.B. and L.R. McMahon, *The contribution of alpha4beta2 and non-alpha4beta2 nicotinic acetylcholine receptors to the discriminative stimulus effects of nicotine and varenicline in mice*. Psychopharmacology (Berl), 2017. **234**(5): p. 781-792.
19. Bolliger, C.T., et al., *Effects of varenicline in adult smokers: a multinational, 24-week, randomized, double-blind, placebo-controlled study*. Clin Ther, 2011. **33**(4): p. 465-77.
20. Gonzales, D., et al., *Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial*. Jama, 2006. **296**(1): p. 47-55.
21. Baker, T.B., et al., *Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial*. Jama, 2016. **315**(4): p. 371-9.
22. Tashkin, D.P., et al., *Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial*. Chest, 2011. **139**(3): p. 591-599.
23. Anthenelli, R.M., et al., *Effects of varenicline on smoking cessation in adults with stably treated current or past major depression: a randomized trial*. Ann Intern Med, 2013. **159**(6): p. 390-400.

24. Anthenelli, R.M., et al., *Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial*. *Lancet*, 2016. **387**(10037): p. 2507-20.
25. Nides, M., *Update on pharmacologic options for smoking cessation treatment*. *Am J Med*, 2008. **121**(4 Suppl 1): p. S20-31.
26. FDA, U. *Public Health Advisory: FDA Requires New Boxed Warnings for the Smoking Cessation Drugs Chantix and Zyban*. 2009.
27. Hughes, J.R., L.F. Stead, and T. Lancaster, *Nortriptyline for smoking cessation: a review*. *Nicotine Tob Res*, 2005. **7**(4): p. 491-9.
28. Hall, S.M., et al., *Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking*. *Arch Gen Psychiatry*, 1998. **55**(8): p. 683-90.
29. Prochazka, A.V., et al., *A randomized trial of nortriptyline for smoking cessation*. *Arch Intern Med*, 1998. **158**(18): p. 2035-9.
30. Gourlay, S.G., L.F. Stead, and N.L. Benowitz, *Clonidine for smoking cessation*. *Cochrane Database Syst Rev*, 2004(3): p. Cd000058.
31. Carrao, J.L., L.B. Moreira, and F.D. Fuchs, *The efficacy of the combination of sertraline with buspirone for smoking cessation. A randomized clinical trial in nondepressed smokers*. *Eur Arch Psychiatry Clin Neurosci*, 2007. **257**(7): p. 383-8.
32. Hughes, J.R., L.F. Stead, and T. Lancaster, *Anxiolytics for smoking cessation*. *Cochrane Database Syst Rev*, 2000(4): p. Cd002849.
33. Schwartz, J.L. and M. Dubitzky, *One-year follow-up results of a smoking cessation program*. *Can J Public Health*, 1968. **59**(4): p. 161-5.
34. Hughes, J.R., L.F. Stead, and T. Lancaster, *Antidepressants for smoking cessation*. *Cochrane Database Syst Rev*, 2007(1): p. Cd000031.
35. Weinberger, A.H., et al., *A double-blind, placebo-controlled, randomized clinical trial of oral selegiline hydrochloride for smoking cessation in nicotine-dependent cigarette smokers*. *Drug Alcohol Depend*, 2010. **107**(2-3): p. 188-95.

36. Kahn, R., et al., *Selegiline transdermal system (STS) as an aid for smoking cessation*. Nicotine Tob Res, 2012. **14**(3): p. 377-82.
37. Killen, J.D., et al., *Failure to improve cigarette smoking abstinence with transdermal selegiline + cognitive behavior therapy*. Addiction, 2010. **105**(9): p. 1660-8.
38. Schnoll, R.A., et al., *A placebo-controlled trial of modafinil for nicotine dependence*. Drug Alcohol Depend, 2008. **98**(1-2): p. 86-93.
39. Stead, L.F. and J.R. Hughes, *Lobeline for smoking cessation*. Cochrane Database Syst Rev, 2012(2): p. Cd000124.
40. Glover, E.D., et al., *A multicenter phase 3 trial of lobeline sulfate for smoking cessation*. Am J Health Behav, 2010. **34**(1): p. 101-9.
41. Rose, J.E., *Nicotine addiction and treatment*. Annu Rev Med, 1996. **47**: p. 493-507.
42. Stead, L.F. and T. Lancaster, *Nicobrevin for smoking cessation*. Cochrane Database Syst Rev, 2006(2): p. Cd005990.
43. Dankwa, E., L. Perry, and A. Perkins, *A double-blind, placebo-controlled study to determine the efficacy of Nicobrevin anti-smoking capsules*. Br J Clin Pract, 1988. **42**(9): p. 359-63.
44. Schmidt, F., *[Medical support of nicotine withdrawal. Report on a double blind trail in over 5000 smokers (author's transl)]*. MMW Munch Med Wochenschr, 1974. **116**(11): p. 557-64.
45. David, S.P., et al., *Systematic review and meta-analysis of opioid antagonists for smoking cessation*. BMJ Open, 2014. **4**(3): p. e004393.
46. Mooney, M.E., et al., *Bupropion and naltrexone for smoking cessation: A double-blind randomized placebo-controlled clinical trial*. Clin Pharmacol Ther, 2016. **100**(4): p. 344-52.
47. Fridberg, D.J., et al., *Naltrexone improves quit rates, attenuates smoking urge, and reduces alcohol use in heavy drinking smokers attempting to quit smoking*. Alcohol Clin Exp Res, 2014. **38**(10): p. 2622-9.

48. Morrison, M.F., et al., *Randomized, controlled, double-blind trial of taranabant for smoking cessation*. Psychopharmacology (Berl), 2010. **209**(3): p. 245-53.
49. Cahill, K. and M.H. Ussher, *Cannabinoid type 1 receptor antagonists for smoking cessation*. Cochrane Database Syst Rev, 2011(3): p. Cd005353.
50. Lancaster, T. and L.F. Stead, *Silver acetate for smoking cessation*. Cochrane Database Syst Rev, 2012(9): p. Cd000191.
51. Zacny, J.P., et al., *Effects of 5-hydroxytryptamine₃ antagonist, ondansetron, on cigarette smoking, smoke exposure, and mood in humans*. Pharmacol Biochem Behav, 1993. **44**(2): p. 387-91.
52. West, R. and P. Hajek, *Randomised controlled trial of ondansetron in smoking cessation*. Psychopharmacology (Berl), 1996. **126**(1): p. 95-6.
53. Melis, M., et al., *PPAR α regulates cholinergic-driven activity of midbrain dopamine neurons via a novel mechanism involving α 7 nicotinic acetylcholine receptors*. J Neurosci, 2013. **33**(14): p. 6203-11.
54. Perkins, K.A., et al., *Initial Evaluation of Fenofibrate for Efficacy in Aiding Smoking Abstinence*. Nicotine Tob Res, 2016. **18**(1): p. 74-8.
55. Ashare, R.L., et al., *Repeated administration of an acetylcholinesterase inhibitor attenuates nicotine taking in rats and smoking behavior in human smokers*. Transl Psychiatry, 2016. **6**: p. e713.
56. Diehl, A., et al., *Rivastigmine reduces tobacco craving in alcohol-dependent smokers*. Pharmacopsychiatry, 2009. **42**(3): p. 89-94.
57. Oncken, C., et al., *Topiramate for smoking cessation: a randomized, placebo-controlled pilot study*. Nicotine Tob Res, 2014. **16**(3): p. 288-96.
58. Anthenelli, R.M., et al., *Preliminary evidence for gender-specific effects of topiramate as a potential aid to smoking cessation*. Addiction, 2008. **103**(4): p. 687-94.
59. Baltieri, D.A., et al., *Effects of topiramate or naltrexone on tobacco use among male alcohol-dependent outpatients*. Drug Alcohol Depend, 2009. **105**(1-2): p. 33-41.

60. Johnson, B.A., et al., *Use of oral topiramate to promote smoking abstinence among alcohol-dependent smokers: a randomized controlled trial.* Arch Intern Med, 2005. **165**(14): p. 1600-5.
61. Anthenelli, R.M., et al., *A Randomized Trial Evaluating Whether Topiramate Aids Smoking Cessation and Prevents Alcohol Relapse in Recovering Alcohol-Dependent Men.* Alcohol Clin Exp Res, 2017. **41**(1): p. 197-206.
62. Isgro, M., et al., *Type A/Type B Alcoholism Predicts Differential Response to Topiramate in a Smoking Cessation Trial in Dually Diagnosed Men.* J Stud Alcohol Drugs, 2017. **78**(2): p. 232-240.
63. Sood, A., et al., *Gabapentin for smoking cessation: a preliminary investigation of efficacy.* Nicotine Tob Res, 2007. **9**(2): p. 291-8.
64. White, W.D., et al., *A randomized, open-label pilot comparison of gabapentin and bupropion SR for smoking cessation.* Nicotine Tob Res, 2005. **7**(5): p. 809-13.
65. Sood, A., et al., *Gabapentin for smoking cessation.* Nicotine Tob Res, 2010. **12**(3): p. 300-4.
66. Prado, E., et al., *N-acetylcysteine for therapy-resistant tobacco use disorder: a pilot study.* Redox Rep, 2015. **20**(5): p. 215-22.
67. Santa Ana, E.J., et al., *D-Cycloserine attenuates reactivity to smoking cues in nicotine dependent smokers: a pilot investigation.* Drug Alcohol Depend, 2009. **104**(3): p. 220-7.
68. Thuerauf, N., et al., *Memantine fails to facilitate partial cigarette deprivation in smokers--no role of Memantine in the treatment of nicotine dependency?* J Neural Transm (Vienna), 2007. **114**(3): p. 351-7.
69. Knackstedt, L.A., et al., *The role of cystine-glutamate exchange in nicotine dependence in rats and humans.* Biol Psychiatry, 2009. **65**(10): p. 841-5.
70. Froeliger, B., et al., *The effects of N-Acetylcysteine on frontostriatal resting-state functional connectivity, withdrawal symptoms and smoking abstinence: A double-blind, placebo-controlled fMRI pilot study.* Drug Alcohol Depend, 2015. **156**: p. 234-42.

71. McClure, E.A., et al., *An open-label pilot trial of N-acetylcysteine and varenicline in adult cigarette smokers*. Am J Drug Alcohol Abuse, 2015. **41**(1): p. 52-6.
72. Tutka, P., *Nicotinic receptor partial agonists as novel compounds for the treatment of smoking cessation*. Expert Opin Investig Drugs, 2008. **17**(10): p. 1473-85.
73. Walker, N., et al., *Cytisine versus nicotine for smoking cessation*. N Engl J Med, 2014. **371**(25): p. 2353-62.
74. Hurt, R.D., et al., *Carbidopa/levodopa for smoking cessation: a pilot study with negative results*. Nicotine Tob Res, 2000. **2**(1): p. 71-8.
75. Jarvik, M.E., et al., *Bromocriptine reduces cigarette smoking*. Addiction, 2000. **95**(8): p. 1173-83.
76. Shahab, L., L.S. Brose, and R. West, *Novel delivery systems for nicotine replacement therapy as an aid to smoking cessation and for harm reduction: rationale, and evidence for advantages over existing systems*. CNS Drugs, 2013. **27**(12): p. 1007-19.
77. Caponnetto, P., et al., *The emerging phenomenon of electronic cigarettes*. Expert Rev Respir Med, 2012. **6**(1): p. 63-74.
78. Noel, J.K., V.W. Rees, and G.N. Connolly, *Electronic cigarettes: a new 'tobacco' industry?* Tob Control, 2011. **20**(1): p. 81.
79. Hartmann-Boyce, J., et al., *Electronic cigarettes for smoking cessation*. Cochrane Database of Systematic Reviews, 2016(9).
80. Hartmann-Boyce, J., et al., *Nicotine vaccines for smoking cessation*. Cochrane Database Syst Rev, 2012(8): p. Cd007072.
81. Tonstad, S., et al., *Niccine(R), a nicotine vaccine, for relapse prevention: a phase II, randomized, placebo-controlled, multicenter clinical trial*. Nicotine Tob Res, 2013. **15**(9): p. 1492-501.
82. Hoogsteder, P.H., et al., *Efficacy of the nicotine vaccine 3'-AmNic-rEPA (NicVAX) co-administered with varenicline and counselling for smoking cessation: a randomized placebo-controlled trial*. Addiction, 2014. **109**(8): p. 1252-9.

83. Killen, J.D., et al., *Nicotine patch and paroxetine for smoking cessation*. J Consult Clin Psychol, 2000. **68**(5): p. 883-9.
84. Covey, L.S., et al., *A randomized trial of sertraline as a cessation aid for smokers with a history of major depression*. Am J Psychiatry, 2002. **159**(10): p. 1731-7.
85. Blondal, T., et al., *Nicotine nasal spray with nicotine patch for smoking cessation: a randomised trial with six year follow up*. Bmj, 1999. **318**(7179): p. 285-8.
86. Niaura, R., et al., *Multicenter trial of fluoxetine as an adjunct to behavioral smoking cessation treatment*. J Consult Clin Psychol, 2002. **70**(4): p. 887-96.
87. Saules, K.K., et al., *Double-blind placebo-controlled trial of fluoxetine in smoking cessation treatment including nicotine patch and cognitive-behavioral group therapy*. Am J Addict, 2004. **13**(5): p. 438-46.
88. Spring, B., et al., *Fluoxetine, smoking, and history of major depression: A randomized controlled trial*. J Consult Clin Psychol, 2007. **75**(1): p. 85-94.
89. Brown, R.A., et al., *Efficacy of sequential use of fluoxetine for smoking cessation in elevated depressive symptom smokers*. Nicotine Tob Res, 2014. **16**(2): p. 197-207.
90. Cinciripini, P.M., et al., *Combined effects of venlafaxine, nicotine replacement, and brief counseling on smoking cessation*. Exp Clin Psychopharmacol, 2005. **13**(4): p. 282-92.
91. Hilleman, D.E., S.M. Mohiuddin, and M.G. Delcore, *Comparison of fixed-dose transdermal nicotine, tapered-dose transdermal nicotine, and buspirone in smoking cessation*. J Clin Pharmacol, 1994. **34**(3): p. 222-4.
92. Cinciripini, P.M., et al., *A placebo-controlled evaluation of the effects of buspirone on smoking cessation: differences between high- and low-anxiety smokers*. J Clin Psychopharmacol, 1995. **15**(3): p. 182-91.
93. Schneider, N.G., et al., *Efficacy of buspirone in smoking cessation: a placebo-controlled trial*. Clin Pharmacol Ther, 1996. **60**(5): p. 568-75.
94. Berlin, I., et al., *A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers*. Clin Pharmacol Ther, 1995. **58**(4): p. 444-52.

95. Biberman, R., et al., *A randomized controlled trial of oral selegiline plus nicotine skin patch compared with placebo plus nicotine skin patch for smoking cessation.* Addiction, 2003. **98**(10): p. 1403-7.
96. George, T.P., et al., *A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation.* Biol Psychiatry, 2003. **53**(2): p. 136-43.
97. Rose, J.E., et al., *Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone.* Clin Pharmacol Ther, 1994. **56**(1): p. 86-99.
98. Covey, L.S., A.H. Glassman, and F. Stetner, *Naltrexone effects on short-term and long-term smoking cessation.* J Addict Dis, 1999. **18**(1): p. 31-40.
99. Wong, G.Y., et al., *A randomized trial of naltrexone for smoking cessation.* Addiction, 1999. **94**(8): p. 1227-37.
100. King, A., et al., *Efficacy of naltrexone in smoking cessation: a preliminary study and an examination of sex differences.* Nicotine Tob Res, 2006. **8**(5): p. 671-82.
101. O'Malley, S.S., et al., *A controlled trial of naltrexone augmentation of nicotine replacement therapy for smoking cessation.* Arch Intern Med, 2006. **166**(6): p. 667-74.
102. Toll, B.A., et al., *Low-dose naltrexone augmentation of nicotine replacement for smoking cessation with reduced weight gain: a randomized trial.* Drug Alcohol Depend, 2010. **111**(3): p. 200-6.
103. King, A.C., et al., *Effects of naltrexone on smoking cessation outcomes and weight gain in nicotine-dependent men and women.* J Clin Psychopharmacol, 2012. **32**(5): p. 630-6.
104. Cahill, K. and M. Ussher, *Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation.* Cochrane Database Syst Rev, 2007(4): p. Cd005353.
105. Westman, E.C., F.M. Behm, and J.E. Rose, *Airway sensory replacement combined with nicotine replacement for smoking cessation. A randomized, placebo-controlled trial using a citric acid inhaler.* Chest, 1995. **107**(5): p. 1358-64.

106. Hymowitz, N. and H. Eckholdt, *Effects of a 2.5-mg silver acetate lozenge on initial and long-term smoking cessation*. Prev Med, 1996. **25**(5): p. 537-46.
107. Jensen, E.J., et al., *Effect of nicotine, silver acetate, and ordinary chewing gum in combination with group counselling on smoking cessation*. Thorax, 1990. **45**(11): p. 831-4.
108. Parsons, A., et al., *A proof of concept randomised placebo controlled factorial trial to examine the efficacy of St John's wort for smoking cessation and chromium to prevent weight gain on smoking cessation*. Drug Alcohol Depend, 2009. **102**(1-3): p. 116-22.
109. Sood, A., et al., *A randomized clinical trial of St. John's wort for smoking cessation*. J Altern Complement Med, 2010. **16**(7): p. 761-7.
110. Sood, A., et al., *S-adenosyl-L-methionine (SAME) for smoking abstinence: a randomized clinical trial*. J Altern Complement Med, 2012. **18**(9): p. 854-9.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Gomez-Coronado, N;Walker, AJ;Berk, M;Dodd, S

Title:

Current and Emerging Pharmacotherapies for Cessation of Tobacco Smoking

Date:

2018-02-01

Citation:

Gomez-Coronado, N., Walker, A. J., Berk, M. & Dodd, S. (2018). Current and Emerging Pharmacotherapies for Cessation of Tobacco Smoking. PHARMACOTHERAPY, 38 (2), pp.235-258. <https://doi.org/10.1002/phar.2073>.

Persistent Link:

<http://hdl.handle.net/11343/283453>