Randomized Clinical Trials Investigating Innovative Interventions for Smoking Cessation in the Last Decade

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Contents

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Abstract

Every year, billions of dollars are spent treating smoking and related conditions, yet smoking-related morbidity and mortality continue to rise. There are currently only three FDA-approved medications for smoking cessation: nicotine replacement therapy, bupropion, and varenicline. Although these medications increase abstinence rates, most individuals relapse following treatment. This chapter reviews clinical trials published within the past 10 years investigating novel smoking cessation pharmacotherapies. Among these pharmacotherapies, some showed promising results, such as cytisine and endocannabinoid modulators, whereas others failed to produce significant effects. More research is needed to develop drugs that produce higher rates of long-term abstinence and to determine which subgroups of patients benefit from a given treatment.

Keywords

Anticonvulsants · Antidepressive agents · Cannabinoid receptor modulators · Cholinergic agents · Randomized controlled trial · Smoking cessation · Smoking cessation agents · Tobacco use disorder

1 Introduction

Smoking addiction, now referred to by the DSM-5 as tobacco use disorder (TUD), is a complex condition that is thought to be caused by a combination of psychosocial and pharmacological factors (Mitchell and Potenza 2014). It is estimated that there are over one billion smokers worldwide. Tobacco-related morbidity is thought to lead to seven million deaths per year, and this number is expected to increase to eight to ten million deaths per year by 2030 (Burki 2015; Forouzanfar et al. 2015; Gowing et al. 2015). Unfortunately, quitting smoking is extremely difficult; less than 5% of quit attempts per year are considered successful despite the fact that 70% of smokers wish to quit (Schauer et al. 2015).

Nicotine is the most addictive ingredient in cigarettes (Le Foll and Goldberg 2006). Nicotine binds to nicotinic cholinergic receptors (nAChRs), which are ligand-gated ion channels. The reinforcing effects of nicotine are mediated through the release of various neurotransmitters including dopamine, which plays a fundamental role in reward, as well as acetylcholine, vasopressin, serotonin, norepinephrine, glutamate, gamma-aminobutyric acid (GABA), and beta-endorphins (David et al. 2014; Le Foll 2013). Researchers are continuously searching for medications that target one or more of these neurotransmitter systems in the hopes of finding new effective smoking cessation aids (Bozinoff and Le Foll 2018).

There are currently three pharmacotherapies for smoking cessation that are approved by the Food and Drug Administration (FDA): nicotine replacement therapy (NRT), bupropion hydrochloride, and varenicline tartrate (Le Foll and George 2007; Prochaska and Benowitz 2016). NRT products include gum, patches, inhalers, nasal and oral sprays, and lozenges, and their main benefits are the reduction of craving and withdrawal symptoms induced by tobacco cessation (Stead et al. 2012). Bupropion hydrochloride acts by blocking nAChRs, as well as norepinephrine and dopamine reuptake, which reduces smoking cessation-induced craving, withdrawal symptoms, and negative mood (Kotlyar et al. 2011; McCarthy et al. 2008). Varenicline tartrate, a selective $\alpha 4\beta 2*$ nicotinic receptor partial agonist (the asterisk indicates the potential presence of other subunits) (Cahill et al. 2013), is thought to be the most effective medication for smoking cessation. Although FDA-approved medications increase abstinence rates, relapse remains the most likely outcome, with abstinence rates of only 20–30% at 1 year posttreatment (Cahill et al. 2007). New pharmacotherapies are needed for TUD in order to achieve higher rates of long-term abstinence.

2 Cholinergic System

The addictive effects of tobacco are thought to arise from activation of nicotinic acetylcholine receptors (nAChRs) in the ventral tegmental area and the nucleus accumbens (Weinberger and Sofuoglu 2009). Hence, a great deal of smoking cessation research has focused on drugs that target nAChRs. However, not all drugs targeting nAChRs act in the same way. For instance, varenicline acts as a

partial agonist at α4β2∗ (Coe et al. 2005), whereas bupropion is a noncompetitive antagonist at α3β2, α4β2∗, and less effectively at α7 (Slemmer et al. 2000). The different nAChR subtypes have been extensively characterized in preclinical studies (Benowitz 2010; Mineur and Picciotto 2008).

2.1 Agonists

In the past decade, three nAChR agonists without FDA approval have been tested for use as smoking cessation aids: dianicline, encenicline, and cytisine. Dianicline is a partial agonist of the α4β2∗ nicotinic acetylcholine receptor subtype. It showed promising effects in Phase I and II studies. However, in a Phase III trial, researchers found no benefit of dianicline treatment on abstinence rates compared to placebo (Tonstad et al. 2011), and the drug was withdrawn from future development. Around the same time, it was shown that binding affinity to α4β2∗ nAChRs is two orders of magnitude lower for dianicline compared to varenicline (Rollema et al. 2010). Similarly, encenicline, an α7 nAChR partial agonist, did not show any benefit for smoking cessation when compared to placebo or when co-administered with nicotine replacement therapy (Schuster et al. 2018).

Cytisine is a partial agonist of α4β2∗ derived from plants of the Leguminosae (Fabaceae) family (Izaddoost et al. 1976). In 1964, cytisine (Tabex®) was marketed as a smoking cessation aid in Central and Eastern Europe (Tutka and Zatonski 2006). However, it still has not been approved in Western countries, except in Canada where it was approved as a natural health product in 2016 (Government of Canada 2018). Cytisine has been shown to be both a beneficial smoking cessation aid and a cost-effective treatment. A typical course of treatment with cytisine lasts 25 days and costs as little as $20, whereas varenicline treatment typically lasts 12 weeks and costs around $500 (Prochaska et al. 2013). Many clinical trials have demonstrated beneficial effects of cytisine, such as one study that found that 10.6% of participants given cytisine were continuously abstinent after 26 weeks, as compared to 1.2% of participants given placebo (Vinnikov et al. 2008). A similar trial was conducted investigating abstinence rates at 12 months (West et al. 2011). Rates of abstinence in the cytisine group were 8.4%, compared to 2.4% in the placebo group. When compared to nicotine replacement therapy, cytisine was found to be superior at 1 week, 1 month, 2 months, and 6 months of follow-up (Walker et al. 2014). It should be noted that over the 6 months, those given cytisine reported more adverse effects, mainly nausea, vomiting, and sleep disorders. The next step will be to determine whether cytisine is as effective as varenicline. Currently, there is an ongoing clinical trial investigating this in Maori smokers (Clinicaltrial.gov identifier NCT02957786) (Walker et al. 2018).

2.2 Antagonists

Mecamylamine is a nonselective and noncompetitive nAChR antagonist (Philip et al. 2012). Earlier smoking cessation trials with mecamylamine have demonstrated mixed results (Glover et al. 2007; Rose et al. 1994, 1996). More recently, researchers reanalyzed the results of a randomized placebo-controlled clinical trial evaluating the use of mecamylamine to treat alcohol use disorder in smokers and non-smokers (Roberts et al. 2018). They found no effect on smoking outcomes. However, it should be noted that motivation to quit smoking was not measured as this study was focused on the treatment of alcohol use disorder; hence participants may not have been interested in quitting smoking.

2.3 Positive Allosteric Modulators and Acetylcholinesterase Inhibitors

Positive allosteric modulators (PAM) of nicotinic acetylcholine receptors have been developed for smoking cessation. JNJ-39393406 is a PAM of the α7 subtype of nAChRs recently developed by Janssen Research and Development LLC. A group of researchers ran two studies, one with healthy smokers ($n = 31$) and another with smokers with schizophrenia ($n = 56$), but both studies were negative (Perkins et al. 2018). JNJ-39393406 did not improve abstinence rates, craving, or withdrawal when compared to placebo. Although this was not a large clinical trial, the researchers concluded that further research is not warranted at this particular dose (100 mg BID).

Two acetylcholinesterase inhibitors have recently been tested for smoking cessation. Galantamine, in addition to being an acetylcholinesterase inhibitor, is also a PAM of the α4β2∗ receptor. A recent 7-week trial randomized participants ($n = 60$) to 8 or 16 mg of galantamine per day or placebo (MacLean et al. 2018). During the pre-quit period, both doses of galantamine reduced urine cotinine levels and smoking in a laboratory choice task compared to placebo, but did not decrease self-reported cigarette smoking. Results following the quit attempt have not yet been published. Another acetylcholinesterase inhibitor, rivastigmine, has also been tested in alcohol-dependent smokers and methamphetamine-dependent smokers. In the alcohol dependence study, participants ($n = 26$) were randomized to either 6 mg/day of rivastigmine or placebo for 4 weeks. Rivastigmine was found to decrease the number of daily cigarettes consumed (−30%), tobacco craving (−18%), and carbon monoxide (CO) levels (−32%) (Diehl et al. 2009). In the methamphetamine dependence study, participants were randomized to 3 or 6 mg of rivastigmine or placebo for 9 days. They found that rivastigmine did not have any effects on smoking measures, but a trend was observed for reduction in urges to smoke (De la Garza and Yoon 2011). However, it should be noted that the sample size was small ($n = 13$), the participants were nontreatment seeking, and the duration of treatment was short. Further studies are necessary to determine whether rivastigmine is effective in smokers without comorbid addiction.

3 Endocannabinoid System

Weight gain is a serious concern for smokers who wish to quit, especially females. It is thought that nicotine increases basal metabolic rate and smoking cessation can lead to increased appetite and decreased energy consumption (Filozof et al. 2004). The current FDA-approved medications are not effective at preventing the weight gain associated with smoking cessation. For example, bupropion and NRT delay weight gain to some extent, but their effects do not last after treatment cessation (Parsons et al. 2009). It would be an asset if one agent could reduce both smoking rates and abstinence-related weight gain.

The endocannabinoid system is one of the central nervous system's neuromodulator systems. It is formed of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and various enzymes responsible for the synthesis or the degradation of the endocannabinoids. The cannabinoid receptors 1 and 2 (CB1 and CB2) are the main cannabinoid receptors which mediate the actions of endocannabinoids as well as the exogenous cannabinoids (Lu and Anderson 2017). Endocannabinoid system modulators facilitate weight loss in obesity (Drewnowski et al. 1995; King et al. 2013) and have also been shown to decrease nicotine self-administration in animal models (Cohen et al. 2002). These medications might be helpful in individuals who have difficulty quitting due to fear of weight gain or in individuals who relapse following smoking cessation-induced weigh gain.

3.1 CB1 Receptor Inverse Agonists

Rimonabant is a CB1 inverse agonist and has been previously used as a treatment for obesity (Curioni and Andre 2006; Sloan et al. 2017). Recently, the results of several large clinical trials for smoking cessation were published (Robinson et al. 2018). An analysis of the pooled data from these three trials ($n = 2097$) found that individuals treated with 20 mg of rimonabant had significantly higher rates of abstinence even at 48 weeks post-quit date compared to placebo (OR = 1.50, 95% CI: 1.03, 2.17) (Robinson et al. 2018). Nevertheless, the rimonabant group showed higher rates of side effects such as nausea, vomiting, diarrhea, and anxiety. The high rate of psychiatric side effects led to the voluntary withdrawal of rimonabant from the European market in 2008.

Other CB1 inverse agonists were also examined for smoking cessation. For example, surinabant was assessed at three different doses, 2.5 mg/day ($n = 199$), 5 mg/day ($n = 204$), or 10 mg/day ($n = 205$) vs. placebo ($n = 202$), during an 8-week treatment phase and 6-week follow-up and was not found to be effective (Tonstad and Aubin 2012). Another CB1 inverse agonist, taranabant, was also ineffective (Morrison et al. 2010). The poor efficacy of CB1 inverse agonists in these studies may have been at least partially due to the unfavorable side effect profile of these medications.

3.2 Cannabidiol

Cannabidiol (CBD), a non-psychoactive exogenous cannabinoid, acts on multiple non-cannabinoid receptors including serotonin 1A (5HT1A), peroxisome proliferator-activated receptor gamma (PPAR γ), and transient receptor potential vanilloid 1 (TRPV1) cation channels (Laprairie et al. 2015). Although CBD was previously thought to antagonize CB1 (Pertwee 2008), recent evidence suggests that it may actually function as a negative allosteric modulator (Tham et al. 2018). In a recent small trial ($n = 24$), smokers were randomized to treatment with cannabidiol (400 μg) or placebo inhalers. Those treated with cannabidiol showed a 40% decrease in the number of cigarettes smoked during the treatment period (1 week) and at follow-up (2 weeks after treatment) compared to those treated with placebo (Morgan et al. 2013). However, this trial was limited by the small sample size, short duration of follow-up, and the use of smoking reduction rather than cessation as an outcome. Nevertheless, given that CBD seems to have a better safety profile than rimonabant (Bergamaschi et al. 2011), further investigation remains worthwhile.

4 Naltrexone

Mu-opioid receptor antagonists may facilitate smoking cessation and weight reduction (Epstein and King 2004; Hutchison et al. 1999; King and Meyer 2000; Lee et al. 2005; Wewers et al. 1998). Naltrexone is a mu-opioid receptor antagonist that is FDA approved to treat alcohol and opioid use disorders. Researchers have considered its use as an adjunctive agent to augment the effect of nicotine replacement and to prevent weight gain following smoking cessation (King et al. 2006; O'Malley et al. 2006).

A recent randomized trial found that naltrexone in combination with NRT ($n = 162$) decreased weight gain and increased quit rates versus NRT with placebo ($n = 154$). The weight gain reduction was observed more in females (King et al. 2012). However, in 2013, a Cochrane review pooled data from 8 trials and concluded that naltrexone (25–100 mg/day) was not effective as a long-term smoking cessation aid either alone or in combination with NRT (RR 0.97; 95% CI 0.76–1.24, 1,213 participants) (David et al. 2013). It should be noted that many trials used nontreatment-seeking smokers and different groups tested different dosages, monitoring processes, and quitting plans, all of which could have affected the end results.

Naltrexone has also been examined in combination with bupropion, as this combination has been approved for weight loss in individuals with obesity. It is thought that weight loss is achieved through dual action: naltrexone decreases food reward by blocking endorphins and bupropion inhibits appetite (Tek 2016). Obese smokers were treated with naltrexone and bupropion in an open-label trial for 24 weeks. The results showed a decrease in tobacco use but no change in weight (Wilcox et al. 2010). A 24-week clinical trial using the combination of naltrexone and bupropion was also conducted in individuals with schizophrenia, who have high

rates of both smoking and obesity (Marder et al. 2004; Morisano et al. 2009). This trial did not show a significant effect of treatment with naltrexone plus bupropion ($n = 11$) over placebo ($n = 10$) for either smoking cessation or weight reduction (Lyu et al. 2018).

5 Lorcaserin

Lorcaserin (Belviq®) is a drug approved by the FDA for weight loss (US Food and Drug Administration 2018a). It is a selective serotonin 5-HT_{2C} receptor agonist. In humans, 5-HT_{2C} receptors are mainly located in the central nervous system, primarily in the choroid plexus, prefrontal cortex, basal ganglia, and hippocampus (Roth et al. 1998). Given that obesity and drug addiction are thought to share similar neurobiological mechanisms (Volkow and Wise 2005), pharmacotherapies that are effective for obesity could potentially be used to treat substance use disorders as well.

In rats, lorcaserin has been found to reduce nicotine self-administration and nicotine-seeking behavior (Higgins et al. 2012; Levin et al. 2011). These favorable results led to the first clinical trial investigating lorcaserin for smoking cessation. A 12-week randomized controlled trial was conducted in which 603 participants were randomized to 10 mg of lorcaserin once a day (QD), 10 mg twice a day (BID), or placebo (Shanahan et al. 2017). At the end of 3 months of treatment, the BID group had a significantly higher abstinence rate compared to QD and placebo groups (15.3% for BID, 8.7% for QD, and 5.6% for placebo). Participants assigned to 10 mg BID of lorcaserin had the highest CO-confirmed abstinence rate, although these results did not reach significance. A single-arm trial investigating a combination of varenicline and lorcaserin for smoking cessation and post-cessation weight gain has also been published (Hurt et al. 2017). Among the 20 participants, 10 achieved prolonged smoking abstinence at the end of 12 weeks of treatment. Waist circumference increased by 0.2 ± 6.0 cm and weight increased by 1.1 ± 3.9 kg. There is also a completed clinical trial evaluating a combination of lorcaserin and the nicotine patch for smoking cessation, but to our knowledge, no data have been published as of yet (Clinicaltrial.gov identifier NCT02906644).

6 Antidepressants

Antidepressants constitute several classes of medication including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs). The idea of treating TUD with antidepressants stemmed from observations that smokers were more likely to have a history of depression than non-smokers and that quitting smoking may lead to depression (Anda et al. 1990; Benowitz and Wilson Peng 2000). There have been even higher levels of interest in antidepressants as smoking cessation aids ever since bupropion (Zyban®), an antidepressant which

inhibits norepinephrine and dopamine reuptake, was approved as a smoking cessation treatment (Richmond and Zwar 2003).

6.1 Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants that function by blocking the reuptake of serotonin in presynaptic nerve terminals (Stahl 1998), thereby increasing synaptic levels of serotonin. There are various SSRIs on the market including fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram. Fluoxetine is the most studied SSRI for smoking cessation. There is evidence that its efficacy may be dependent on the population studied. For example, smokers with symptoms of depression or past history of major depressive disorder have been shown to benefit most from fluoxetine (Blondal et al. 1999; Dalack et al. 1995), although not all studies have found long-term efficacy (Spring et al. 2007). Nonetheless, these studies led researchers to focus on fluoxetine as a treatment for smokers with depressive symptoms.

Within the past decade, two clinical trials have been completed using fluoxetine for smoking cessation, both directed at smokers with depressive symptoms. Researchers evaluated whether administration of fluoxetine for longer periods prior to the target quit date would improve abstinence rates (Brown et al. 2014). They found that administering fluoxetine for 8 weeks instead of 2 weeks prior to the target quit date was more beneficial. However, the decrease in point prevalence abstinence was more evident at 6-month follow-up than 12-month follow-up, indicating a potential lack of long-term effectiveness. Another study found that treatment with fluoxetine 8 weeks prior to the target quit date did not affect abstinence rates compared to placebo (Minami et al. 2014). However, this study found that fluoxetine treatment reduced pre-quit depressive symptoms and craving in women and withdrawal-related negative affect in men, suggesting potential sex-specific effects.

6.2 Monoamine Oxidase Inhibitors

Monoamine oxidases (MAO) are enzymes that metabolize monoamine and indolamine neurotransmitters (e.g., dopamine, serotonin, norepinephrine) leading to their inactivation (Fiedorowicz and Swartz 2004). MAOs are divided into two subtypes, MAO-A and MAO-B. MAO-A selectivity metabolizes norepinephrine, serotonin, epinephrine, and dopamine, whereas MAO-B selective metabolizes dopamine and β-phenylethylamine (Krishnan 2007). Studies have shown smokers to have reduced MAO activity compared to non-smokers (Lewis et al. 2007; Rose et al. 2001). The rationale for using MAO inhibitors in smoking cessation is to mimic the reduced enzymatic activity found in smokers, which was hypothesized to facilitate quitting.

Selegiline, a selective inhibitor of monoamine oxidase B that is currently used to treat treatment-resistant depression (US Food and Drug Administration 2018b) and Parkinson's disease (US Food and Drug Administration 2018c), has been tested as a smoking cessation aid. Oral selegiline was initially shown to improve abstinence rates when compared to placebo or when used in conjunction with nicotine replacement therapy (NRT) (Biberman et al. 2003; George et al. 2003). However, these results are inconsistent with more recent trials. One trial testing oral selegiline for 8 weeks found that subjects given placebo had numerically higher rates of abstinence at the end of treatment (16% for selegiline and 20% for placebo) (Weinberger et al. 2010). Transdermal selegiline was also found to have no benefit in two other trials (Kahn et al. 2012; Killen et al. 2010). Most recently, EVT302, a new monoamine oxidase B inhibitor, was tested in a Phase II trial. EVT302 showed no superiority over placebo. Administering a nicotine patch along with EVT302 also did not show any additional benefit (Berlin et al. 2012).

6.3 Tricyclic Antidepressants

Tricyclic antidepressants are another class of antidepressant that affects serotonin and norepinephrine signaling (Feighner 1999). One particular tricyclic antidepressant, nortriptyline, has been studied extensively and is approved as a smoking cessation aid in New Zealand (Hughes et al. 2014). A meta-analysis of six clinical trials demonstrated a significant benefit of nortriptyline monotherapy on long-term smoking cessation rates compared to placebo (Hughes et al. 2014). More recently, two clinical trials were completed testing nortriptyline in conjunction with NRT. One study ($n = 901$) found that although both individual therapies were effective, combining the two treatments did not provide further benefits (Aveyard et al. 2008). Another study in a prison population ($n = 425$) also found no increased benefit of combining nortriptyline with NRT (Richmond et al. 2013). When these recent trials were analyzed together with two older but similar trials, there was insufficient evidence to suggest that the combination of nortriptyline and NRT was superior to NRT monotherapy (Hughes et al. 2014).

6.4 Nontraditional Antidepressants

Two nontraditional antidepressants, available primarily as supplements, have been tested for smoking cessation in healthy smokers. St. John's wort is an herbal supplement that is thought to inhibit the reuptake and metabolism of norepinephrine, dopamine, and serotonin (Butterweck 2003). In mice, St. John's wort decreased signs of nicotine withdrawal (Catania et al. 2003). However, when tested in a randomized clinical trial, various doses of St. John's wort did not increase smoking abstinence rates or decrease nicotine withdrawal when compared to placebo (Sood et al. 2010a). The dietary supplement, S-adenosyl-L-methionine (SAMe), is also thought to increase dopamine, norepinephrine, and serotonin levels (Sood et al.

2012) and is used as an antidepressant. When tested for smoking cessation, it was found that SAMe, like St. John's wort, did not increase abstinence rates or decrease tobacco withdrawal (Sood et al. 2012).

7 The Noradrenergic System

Preclinical studies indicate that the noradrenergic system may play a critical role in mediating nicotine reinforcement and nicotine seeking (Forget et al. 2010). Noradrenergic modulators such as labetalol, clonidine, and guanfacine have shown some success at decreasing nicotine craving in human laboratory paradigms (McKee et al. 2015; Sofuoglu et al. 2003) and some clinical trials (Gourlay et al. 2004). Clonidine is a centrally acting α2-adrenergic receptor agonist which lowers heart rate and peripheral resistance. A placebo-controlled trial testing clonidine showed weak evidence for its use as a smoking cessation aid based on abstinence results at 12 weeks of treatment (Gourlay et al. 2004). Side effects such as dizziness, dry mouth, and postural hypotension might limit its use. Doxazocin is an α1-adrenergic receptor antagonist. Its ability to reduce alcohol and cocaine use has been shown in prior studies (Kenna et al. 2016; O'Neil et al. 2013; Shorter et al. 2013). In a pilot study, titrated doses of doxazocin from 4–8 mg/day over 21 days showed a significant reduction in stress-precipitated smoking lapse and tobacco craving compared to placebo (Verplaetse et al. 2017). Large randomized controlled trials (RCTs) with longer follow-up duration are needed to investigate noradrenergic modulators as smoking cessation aids.

8 Anti-epileptic Drugs

8.1 Gabapentin and Pregabalin

Gabapentin is a drug that binds to the α_2-δ subunit of voltage-gated calcium channels and reduces the release of neuronal glutamate. It is also thought to increase the concentration of GABA in the brain (Sood et al. 2007). The clinical evidence for gabapentin's use as a smoking cessation aid is limited. One study found bupropion to be associated with higher abstinence rates compared to gabapentin (White et al. 2005). An open-label study investigated the effects of 8 weeks of gabapentin 600 mg 3 times/day and found an abstinence rate of 24% at 6 months and a significant decrease in the number of cigarettes smoked compared with baseline (Sood et al. 2007). However, a follow-up study that compared two doses of gabapentin, 600 mg 3 times/day or 900 mg 3 times/day, to placebo found no significant difference in abstinence rates between groups at 12 weeks posttreatment (Sood et al. 2010b). Pregabalin, like gabapentin, also binds to voltage-gated calcium channels and has been tested as a smoking cessation aid. A double-blind study compared 300 mg/day of pregabalin to placebo for a 4-day duration and found no benefit on smoking behavior but some reduction in withdrawal symptoms (Herman et al. 2012).

Unfortunately, this trial was of insufficient duration to determine whether pregabalin has any clinical utility.

8.2 Topiramate and Zonisamide

Topiramate is an FDA-approved anticonvulsant and prophylactic treatment for migraine. It has multiple mechanisms of action. It antagonizes glutamatergic receptors, inhibits sodium and L-type calcium channels, and increases GABAergic neurotransmission via GABA-A receptors (Johnson 2004). These actions have been postulated to counterbalance the effects of nicotine, although subjective effects of nicotine are not affected by topiramate (Le Foll et al. 2008a). In 2008, the first randomized, double-blind, placebo-controlled trial investigating topiramate for smoking cessation found sex-specific effects, such that men taking topiramate were almost 16 times more likely to quit smoking compared to women receiving treatment (Anthenelli et al. 2008). A subsequent three-arm pilot study comparing the effects of topiramate and NRT, topiramate monotherapy, and placebo found that topiramate in conjunction with NRT increased continuous abstinence rates compared to placebo (37% vs. 5%, respectively) (Oncken et al. 2014). Topiramate monotherapy also produced higher abstinence rates compared to placebo, but this did not reach significance. However, since there was no NRT monotherapy group, it is unclear if topiramate plus NRT is superior to NRT alone. Several studies testing topiramate in men concurrently diagnosed with alcohol use disorder and TUD have also been conducted. A 12-week trial comparing topiramate (300 mg/day) to naltrexone (50 mg/day) and placebo found reductions in cigarettes smoked per day in the topiramate versus placebo groups and a trend for greater effect in the topiramate versus naltrexone group (Baltieri et al. 2009). On the other hand, a trial with 129 alcohol-dependent smokers who were given topiramate (200 mg/day) or placebo for 12 weeks found no effects on smoking cessation or alcohol relapse (Anthenelli et al. 2017). Zonisamide is an anti-epileptic drug that functions similarly to topiramate but has less adverse side effects (Verrotti et al. 2013). One trial tested a 300 mg dose in combination with varenicline for 10 weeks (Dunn et al. 2016). The combination of zonisamide and varenicline decreased self-reported smoking, nicotine withdrawal, and craving compared to varenicline and placebo, but did not produce any significant differences in cotinine measurements.

9 Gamma-Aminobutyric Acid (GABA) Receptors

Baclofen is a GABA-B receptor agonist that is FDA approved for the treatment of spasticity and has also been extensively studied as a treatment for alcohol use disorder. It has been suggested that this medication may be effective as a smoking cessation aid (Le Foll et al. 2008b; Malcolm 2003; Markou et al. 2004). A 9-week, double-blind, placebo-controlled trial in treatment-seeking smokers showed that 80 mg/day of baclofen reduced the number of cigarettes smoked per day compared

to placebo (Franklin et al. 2009). However, there was a high rate of non-completion in this trial. Currently, the same group is running a Phase II trial investigating the effects of baclofen on brain and behavior in cigarette smokers (ClinicalTrials.gov identifier NCT01821560). The study has been completed, but to our knowledge, results have not yet been published. Another single-arm trial tested baclofen (60 mg/d) in combination with bupropion (300 mg/day) for 7-week duration (White et al. (2011). Eleven out of the 20 participants maintained continuous abstinence over the last 4 weeks of treatment. These preliminary results show early promise for baclofen as a smoking cessation aid, but further studies are warranted.

10 Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

GLP-1 is involved in glucose homeostasis. It functions by increasing insulin secretion and decreasing glucagon release in the periphery (Holst and Seino 2009). GLP-1 also acts centrally on receptors in the hypothalamus and brain stem to produce hypoglycemic effects (Gutniak et al. 1992; Matsuyama et al. 1988). GLP-1 agonists are therefore used as weight control agents for obese diabetic and nondiabetic patients. Preclinical studies indicate that GLP-1 receptor agonists attenuate the substance-induced reward effects of nicotine (Egecioglu et al. 2013a) and other drugs of abuse (Egecioglu et al. 2013a, b, c; Erreger et al. 2012; Graham et al. 2013). This may be due to the fact that GLP-1 receptors are also expressed in the mesolimbic dopamine reward system (Merchenthaler et al. 1999) and may be involved in reward signaling induced by various substances of abuse. Studies showed that the administration of a GLP-1 receptor agonist blunted the rewarding and reinforcing effects of drugs of abuse (Alhadeff et al. 2012). Exenatide, a GLP-1 agonist and a treatment for type 2 diabetes mellitus, is currently being tested as a smoking cessation aid in prediabetic individuals who are overweight ($n = 90$). All smokers received transdermal NRT and behavioral counseling during the 6-week study period (2 weeks of treatment before quit day and 4 weeks after). No results have been published as of yet (ClinicalTrials.gov identifier NCT02975297). There is also an ongoing clinical trial investigating the effects of Dulaglutide, a GLP-1 receptor agonist, on smoking cessation (Clinicaltrial.gov identifier NCT03204396).

11 Statins

Statins are 3-hydroxy-3-methyl-glutaryl-coaenzyme A (HMG CoA) reductase inhibitors that are used to treat hypercholesterolemia (Law and Rudnicka 2006). Statins reduce nicotine-induced reinstatement in animals, although the mechanism for this remains unclear (Chauvet et al. 2016). Only one study has tested a statin for smoking cessation in humans. A 3-month placebo-controlled RCT ($n = 118$) found no effect of 40 mg of simvastatin on craving, number of cigarettes smoked per day, or sustained abstinence. However, the authors suggest that this may have been due to

differences in simvastatin brain penetration between animals and humans (Ingrand et al. 2018); therefore studying statins with greater brain penetrance may prove worthwhile.

12 Stimulants and Atomoxetine

12.1 Attention Deficit Hyperactivity Disorder (ADHD) Medications

Individuals with ADHD are at higher risk of developing nicotine dependence and have lower rates of smoking cessation (Pomerleau et al. 1995). The main treatments for ADHD in all age groups are stimulants such as methylphenidate-based and amphetamine-based products (Faraone and Buitelaar 2010; Faraone and Glatt 2010). Two trials have tested stimulants in smokers with ADHD. The first study randomized smokers with ADHD to 72 mg/day of methylphenidate ($n = 127$) or placebo ($n = 128$) for 11 weeks. During the study, brief weekly individual smoking cessation counseling and 21 mg/day nicotine patches were provided. Unfortunately, methylphenidate treatment did not increase smoking cessation rates in this trial (Winhusen et al. 2010). Another trial randomized smokers with ADHD to 70 mg/day of lisdexamfetamine, an amphetamine prodrug, plus NRT, or placebo plus NRT. Lisdexamfetamine significantly reduced ADHD symptoms but did not reduce smoking abstinence rates compared to placebo (Kollins et al. 2014). Therefore, stimulant treatment in combination with NRT has not been found to be effective in smokers with ADHD to date, and it is not known if they provide any efficacy in smokers without ADHD.

12.2 Atomoxetine

Atomoxetine is another medication used to treat ADHD that functions as a noradrenaline reuptake inhibitor (Garnock-Jones and Keating 2009). A small trial investigated atomoxetine in nontreatment-seeking smokers with ADHD ($n = 15$) in experimental laboratory sessions. Atomoxetine reduced nicotine withdrawal symptoms after overnight abstinence (Gehricke et al. 2011). Another human laboratory study in nontreatment-seeking smokers ($n = 50$), which employed a placebo-controlled crossover design, found reduced withdrawal symptoms under the atomoxetine condition (Ray et al. 2009). Finally, a 14-day double-blind trial that treated smokers diagnosed with schizophrenia ($n = 12$) with atomoxetine (0, 40, or 80 mg/day) found that treatment with atomoxetine led to a 22% decrease in the number of cigarettes smoked per day (Sacco et al. 2009). However, it is not clear whether atomoxetine could be used to reduce smoking rates for a sustained period of time.

12.3 Modafinil

Modafinil is a medication that is used to promote wakefulness in individuals with daytime sleepiness (Ballon and Feifel 2006). It was thought that modafinil's putative cognitive enhancing effects could reduce nicotine withdrawal symptoms and improve quit rates (Lerman et al. 2002). A group of researchers tested modafinil (200 mg/day) versus placebo for smoking cessation in treatment-seeking smokers ($n = 157$) for 8 weeks. Interim analyses were negative. Moreover, the group treated with modafinil showed more abstinence-induced negative mood and withdrawal symptoms. Therefore, the trial was discontinued, and it was concluded that modafinil is not a promising smoking cessation aid (Schnoll et al. 2008).

13 N-Acetylcysteine

N-Acetylcysteine (NAC) is a cysteine prodrug used to treat acetaminophen overdose. In the central nervous system, NAC is converted to cystine (Olive et al. 2012), extracellular cystine is then exchanged for intracellular glutamate, thereby leading to higher levels of extracellular glutamate (Baker et al. 2002). NAC was initially studied as a smoking cessation aid due to emerging evidence that glutamate signaling contributed to addiction (Kalivas et al. 2009). For example, preclinical work found that glutamate reduced the rewarding effects of nicotine and decreased withdrawal (Kenny et al. 2003; Liechti et al. 2007).

In 2009, the first placebo-controlled human study investigating NAC for smoking cessation found decreased cigarette smoking in the NAC versus the placebo group, but no differences in CO levels (Knackstedt et al. 2009). Shortly afterward, a small human laboratory study found that participants in the NAC arm rated cigarettes as less rewarding than in the placebo arm (Schmaal et al. 2011). A 12-week double-blind randomized control trial in participants with TUD found that treatment with NAC significantly reduced the number of cigarettes smoked and CO levels. Also, 47.1% of participants treated with NAC quit smoking compared to 21.4% of participants given placebo (Prado et al. 2015). A single-arm pilot trial ($n = 19$) using a combination of NAC (2.4 g/day) and varenicline (2 mg/day) for 4 weeks showed a significant decrease in the number of cigarettes smoked at the screening visit (16 ± 2) compared to the follow-up visit (5 ± 1). However, point prevalence abstinence rates at the end of the treatment remained low. Despite these preliminary results, studies testing NAC to date have employed small samples, short follow-up duration, and variable doses of NAC. Large clinical trials of longer duration need to be conducted before NAC can be used for treatment of TUD.

14 N-Methyl-D-Aspartate (NMDA) Receptors

N-methyl-D-aspartate (NMDA) receptors are thought to modulate drug self-administration and relapse (Kenny et al. 2009; Trujillo 1995) and could represent a potential target for smoking cessation. Preclinical work has shown that GW468816, a selective antagonist at the glycine site on NMDA receptors, prevents nicotine relapse in short- and long-term models of smoking cessation. Despite these promising preclinical findings, a double-blind, placebo-controlled trial in humans demonstrated that GW468816 had no effect on abstinence rates at the end of 5 weeks of treatment (Evins et al. 2011). D-cycloserine, a partial NMDA agonist, is an FDA-approved antibiotic used for the treatment of tuberculosis (US Food and Drug Administration 2018d). It has been studied for its possible role in enhancing cue exposure therapy in the treatment of addictions (Elrashidi and Ebbert 2014). However, three trials found no benefit to adding D-cycloserine to psychotherapy for smoking cessation (Kamboj et al. 2012; Santa Ana et al. 2009; Yoon et al. 2013). Currently, there is an ongoing clinical trial evaluating the effect of D-cycloserine on smoking cessation in motivated smokers with panic attacks (Clinicaltrial.gov identifier NCT01944423).

15 Progesterone

Progesterone is a steroid hormone that is synthesized in the ovaries and adrenal glands (Lynch and Sofuoglu 2010). Progesterone has been shown to interact with multiple receptors such as GABA-A and nicotinic cholinergic receptors (Lynch and Sofuoglu 2010; Pereira et al. 2002). In preclinical studies, female rats were more motivated for nicotine when progesterone levels were low, and nicotine self-administration decreased when females were pregnant with high levels of progesterone (Lesage et al. 2007; Lynch 2009). Clinical work has been limited, but there is some evidence for progesterone as a smoking cessation aid for both men and women. In one study, researchers gave participants a single 200 mg dose of progesterone or placebo followed by intravenous (IV) nicotine (Sofuoglu et al. 2009). They found that those given progesterone rated the nicotine as having worse effects, had lower levels of "drug liking," and a decreased urge to smoke. Another study examined the effects of 200 or 400 mg/day of progesterone compared to placebo on smoking urges and behaviors (Sofuoglu et al. 2011). They found that 400 mg of progesterone reduced smoking urges, but did not affect ad libitum smoking behavior. A 12-week randomized, double-blind, placebo-controlled, trial was conducted in which 46 abstinent postpartum females were given either 400 mg/day of progesterone or placebo. This study found that participants given progesterone had a higher prevalence of abstinence at 4 weeks (Allen et al. 2016). Researchers also looked at the effect of 400 mg/day of progesterone on women who had achieved abstinence during pregnancy (Forray et al. 2017). They were given progesterone treatment or placebo immediately after delivery for 8 weeks. Women in the active treatment arm were 1.8 times more likely to be abstinent at week 8, and the time to

relapse was longer (10 vs. 4 weeks), although this finding did not reach statistical significance. There is an ongoing clinical trial assessing the combination of progesterone and nicotine replacement therapy for smoking cessation (Clinicaltrial.gov identifier NCT02685072). This trial is also fairly small; studies that are more adequately powered will be needed to determine if progesterone treatment can be used on a larger scale.

16 Conclusion

Every year, billions of dollars are spent treating smoking and related comorbidities (Goodchild et al. 2018). In spite of this, abstinence rates following pharmacotherapy remain low. A deeper understanding of the complex relationship between the cholinergic system and other neurotransmitter systems will be necessary in order to discover novel treatment targets for TUD. Among the pharmacotherapies investigated in the past 10 years, some candidates show promising results such as cytisine and endocannabinoid modulators, whereas others failed to produce significant effects. However, many trials have been limited by small sample sizes and short duration of follow-up. Larger trials that monitor long-term abstinence rates are necessary.

It is unlikely that one medication will benefit all smokers due to individual variability in neurochemistry and behavior. More research will be needed to determine how to tailor specific pharmacotherapies to subpopulations of smokers such as smokers with obesity, mental illnesses, and other comorbidities with a consideration of possible sex differences. It could also be of interest to investigate if treatment using a combination of drugs yields any benefit. Hopefully such research will provide clinicians with an improved pharmacological arsenal which can be used to curb the growing burden of nicotine addiction.

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