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Pharmacotherapy for smoking cessation: pharmacological principles and clinical practice

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Strategies for assisting smoking cessation include behavioural counselling to enhance motivation and to support attempts to quit and pharmacological intervention to reduce nicotine reinforcement and withdrawal from nicotine. Three drugs are currently used as first line pharmacotherapy for smoking cessation, nicotine replacement therapy, bupropion and varenicline. Compared with placebo, the drug effect varies from 2.27 (95% CI 2.02, 2.55) for varenicline, 1.69 (95% CI 1.53, 1.85) for bupropion and 1.60 (95% CI 1.53, 1.68) for any form of nicotine replacement therapy. Despite some controversy regarding the safety of bupropion and varenicline, regulatory agencies consider these drugs as having a favourable benefit/risk profile. However, given the high rate of psychiatric comorbidity in dependent smokers, practitioners should closely monitor patients for neuropsychiatric symptoms. Second-line pharmacotherapies include nortriptyline and clonidine. This review also offers an overview of pipeline developments and issues related to smoking cessation in special populations such as persons with psychiatric comorbidity and pregnant and adolescent smokers.

Introduction

Tobacco addiction is currently considered a chronic disorder that accounts for nearly half a million premature deaths each year in the US alone [1–3] and nearly 6 million people worldwide and causes hundreds of billions of dollars of economic damage [4]. It is predicted that smoking will be responsible for approximately 1 billion smoking-related deaths during the 21st century [5]. Quitting at any age reduces the overall risk of morbidity and mortality [6, 7]. Article 14 of the Framework Convention on Tobacco Control states that every country should implement and provide smoking cessation assistance [8]. Seventy percent of smokers report that they would like to quit, and every year, 40% do quit for at least 1 day [9]. Some highly addicted smokers make serious attempts to quit but are unable to stop for longer than several hours [10]. Finally, approximately 80% of smokers who attempt to quit on their own return to smoking within 1 month, and only 3% of smokers quit successfully each year [9]. Despite the continuing debate over the legitimacy of using resources for individual smoking cessation instead of policy measures and interventions [11–14], the cost-effectiveness of smoking cessation programmes has been consistently confirmed [15–17].

Strategies for helping smokers to quit include behavioural counselling to enhance motivation and to support attempts to quit and pharmacological intervention to reduce nicotine reinforcement and the withdrawal symptoms of cessation of tobacco use [18]. Simple advice to stop smoking results in an increased rate of quitting [1, 3, 19], and counselling increases abstinence rates [20] as a function of time spent with the patient [1]. A minimum intervention for tobacco addiction includes several steps (the 5 As): ask, advise, assess, assist and arrange [3].

Three drugs are currently marketed as first line pharmacotherapy for smoking cessation, nicotine replacement therapy, bupropion hydrochloride (sustained release) and varenicline tartrate [1, 3]. These drugs are, on average, rated as satisfactory by users, with a preference for varenicline among those who tried all three medications [21]. Clonidine and nortriptyline have been proposed as second line pharmacotherapies [1, 3].

Nicotine replacement therapy

Although the potential role of alkaloids other than nicotine has not been ruled out [22], nicotine is considered to be the main tobacco compound that causes and sustains addiction to tobacco [23]. Nicotine replacement therapy (NRT) was the first proven effective medication for the treatment of tobacco addiction and remains a first line pharmacotherapy in helping smokers quit [24]. Nicotine administration has been shown to reverse nicotine/tobacco withdrawal symptoms and the craving to smoke experienced by smokers in the days and weeks following smoking cessation [25]. NRT has also been shown to reduce the reinforcing effects of smoking [26], and it provides an alternative source for some of its reinforcing and cognitive effects [26]. Depending on the country, NRT is marketed either as a buccal absorption product (gum, lozenge, nasal spray, inhaler or sublingual tablet) or as a transdermal patch [27]. NRT, which can be purchased over the counter in many countries, is the only non-prescription drug shown to be effective for smoking cessation. Other nicotine delivery systems are currently being developed [28–31]. The multiple formulations of NRT offer smokers a choice regarding the route of administration, which may have a positive influence on adherence to treatment [32] (Figure 1).

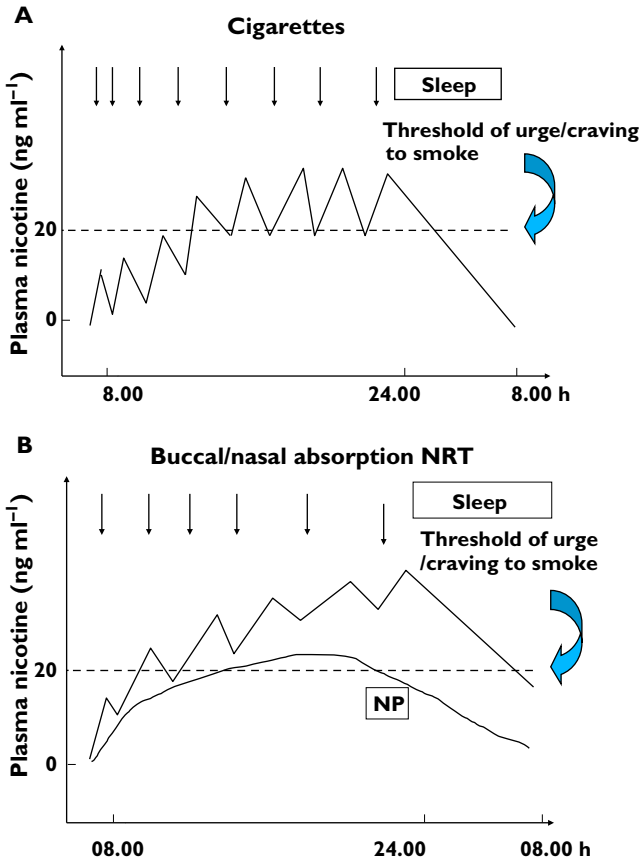

Figure 1

Schematic presentation of plasma nicotine concentrations in venous blood of a smoker over a 24 h period (A) and in an abstinent smoker using nicotine patch (NP) and buccal/nasal absorption nicotine replacement products (B). Combination of NP with rapid, buccal/nasal absorption NRT leads to a higher area under the plasma nicotine concentration curve and peak nicotine concentrations. These result in more time spent above the craving/urge to smoke plasma nicotine concentration threshold and a better mimicking of self-titrated nicotine peaks. (With permission from Journal of Chronic Obstructive Pulmonary Disease, Reference Foulds *et al.* [26])

Pharmacokinetics of nicotine replacement therapies

The bioavailability of nicotine by cigarette smoke inhalation is close to 100% due to the large absorption surface of the lungs and to nicotine's direct delivery to the brain through the pulmonary arteries and heart-carotid circulation. The bioavailability of nicotine by NRTs is much less than that of cigarette smoke [27]. Depending on the brand, the transdermal patch system offers a continuous release of nicotine over 16 or 24 h (Figure 1). By contrast, oral (i.e. buccal absorption) formulations are short acting, the dose can be self-titrated and, thus, time-adjusted according to the patient's needs [32]. Hence, oral NRTs provide smokers with a coping strategy when cigarette cravings occur [26]. Because the available delivery systems do not reproduce the rapid increase and high arterial plasma and brain concentration of nicotine achieved through inhalation of cigarette smoke, NRTs only partially eliminate withdrawal symptoms [32].

Therapeutic efficacy of nicotine replacement therapies

In terms of tobacco abstinence, the efficacy of NRTs varies depending on the formulation, duration and dosage. Risk ratios range from 1.43 (95% CI 1.33, 1.43) to 2.02 (95% CI 1.49, 3.73) (see Table 1) [1, 3, 33]. Improvement of the efficacy of NRT seems possible by combining the transdermal patch with an oral formulation that permits *ad libitum* nicotine delivery [34]. Combined NRT formulations have been shown to result in higher abstinence rates than single NRT in some, [1, 3] though not all [35], meta-analyses. NRT is usually started the day of the programmed quit date. Although considered safe, nicotine preloading (i.e. NRT before a quit date) showed conflicting efficacy results [36–38]. Some evidence suggests that NRT can be used with the goal of smoking reduction as an intermediate step for complete and long term abstinence [39]. A recent study by Alpert *et al.* [41], which received attention from numerous media outlets, concluded that NRT is no more effective in helping people to stop smoking long term – that is, after having stopped its use – than trying to quit on their own. Hughes *et al.* [40]

Table 1

Efficacy of monotherapies for smoking cessation. Summary of Cochrane reviews' findings on the efficacy of medications for smoking cessation

Medication	Number of studies (subjects)	Relative risk (95% CI)
Varenicline (2 mg day^{-1}) *vs.* placebo	15	2.27 (2.02, 2.55)
Varenicline (2 mg day^{-1}) *vs.* bupropion	3	1.52 (1.22, 1.88)
Varenicline (2 mg day^{-1}) *vs.* NRT	2	1.13 (0.94, 1.35)
NRT (any form) *vs.* control	NA	1.58 (1.50, 1.66)
Nicotine gum *vs.* control	53	1.43 (1.33, 1.53)
Nicotine patch *vs.* control	41	1.66 (1.53, 1.81)
Nicotine inhaler *vs.* control	4	1.90 (1.36, 2.67)
Oral tablet/lozenges *vs.* control	6	2.00 (1.63, 2.45)
Nicotine nasal spray *vs.* control	4	2.02 (1.49, 3.73)
Bupropion SR *vs.* placebo	36	1.69 (1.53, 1.85)
Nortriptyline *vs.* placebo	6 (975)	2.03 (1.48, 2.78)
Clonidine *vs.* placebo	6	1.63 (1.22, 2.18)

Adapted from Stead *et al.* [33], Hughes *et al.* [53], Cahill *et al.* [67], Gourlay *et al.* [93].

argued convincingly that the conclusions of Alpert *et al.* [41] were largely overstated and that the study had an inherent methodological bias. In particular, testing the efficacy of NRT during a relapse that occurs years after its use is not an appropriate evaluation of the effectiveness of NRT [40].

Smoking cessation is frequently associated with weight increase [42]. NRT has been shown to limit post-cessation weight gain during the active treatment phase, an effect that does not persist after the termination of treatment [43].

Safety and tolerability of nicotine replacement therapies

The safety profile of NRT is favourable and probably the best among the three first line medications for smoking cessation. The possible adverse effects of night time transdermal nicotine administration, including nightmares, insomnia or EEG changes, have been debated [44, 45]. Transdermal patches can cause mild skin irritation at the placement site; nicotine gum may cause mouth soreness, dyspepsia, hiccups, and jaw pain; the nicotine inhaler may cause mouth and throat irritation and coughing; the nicotine lozenge can lead to mouth and throat irritation and hiccups; and the nicotine nasal spray may cause throat and nasal irritation and a runny nose [32].

There is some concern that buccal absorption NRTs are used longer than intended because of persistent nicotine dependence. Persistent use of nicotine gum was first reported in 1988 [46] and later confirmed [47]. However, it noteworthy that after more than 30 years of wordlwide marketing, there has been no post-marketing alert signal regarding the safety of NRT.

Bupropion

Bupropion SR was the first licensed non-nicotinic pharmacological therapy for smoking cessation. Bupropion was first approved as an atypical antidepressant in the USA and other countries. Its development for tobacco addiction treatment was based on the observation that it reduced craving for cigarettes [48]. Bupropion is a beta-phenylethylamine derivative, which explains its stimulant property. It preferentially blocks norepinephrine and dopamine re-uptake in the mesolimbic system and the nucleus accumbens [49] and is also an antagonist of nicotinic receptors. Hence, it blocks the reinforcing effects of nicotine to a certain extent [50, 51]. Bupropion is metabolized into three active metabolites by cytochrome 2B6.

Therapeutic efficacy of bupropion

The recommended dosage of bupropion is 150 mg twice daily. Because steady-state plasma concentrations of bupropion are obtained 5 to 8 days after treatment initiation, smokers treated with bupropion should aim to quit approximately 1 week after the start of treatment [52].

Several meta-analyses have confirmed the efficacy of bupropion [1, 3, 53]. The Cochrane review has shown a risk ratio over placebo of 1.69 (95% CI 1.53, 1.85) [53] (see Table 1). Bupropion has been shown to decrease nicotine/tobacco withdrawal symptoms and cigarette cravings [54] and to reduce post-cessation weight gain, at least until the end of treatment [43]. One meta-analysis has shown a significant increase of efficacy when bupropion is added to standard nicotine patch therapy [3], a result not clearly reported in the Cochrane review [53].

Safety and tolerability of bupropion

The most common adverse effects associated with the use of bupropion SR at the recommended dosage of 150 mg twice daily in clinical trials included insomnia, headache, dry mouth, nausea and anxiety [55]. Insomnia and anxiety are also recognized symptoms of nicotine/tobacco withdrawal. Only insomnia and dry mouth occurred significantly more frequently with bupropion SR than with placebo. Infrequent but clinically important adverse reactions to bupropion SR include seizures and hypersensitivity reactions. The most common adverse effects (insomnia and dry mouth) are generally transient and often resolve quickly without therapeutic intervention. They can be managed, if necessary, by dose reduction. Although data are limited, bupropion is considered safe for use in patients with cardiovascular disease [56] or COPD [57]. Bupropion SR is contraindicated in smokers with known hypersensitivity to the drug or its excipients, those with current or previous seizure disorders, bulimia, anorexia nervosa and those taking monoamine oxidase inhibitors. Furthermore, bupropion SR should not be administered while patients are undergoing abrupt withdrawal from alcohol or benzodiazepines, as it carries a risk of seizures [55].

It should be noted, that soon after the marketing of bupropion SR for smoking cessation, a high rate of neuropsychiatric adverse reactions was reported. Using post-marketing spontaneous reporting data, a recent study showed an increased risk of reported depression and suicidal/self-injurious behaviour with bupropion compared with NRT [58]. However, a meta-analysis of controlled studies did not shown any increase in suicidal behaviour with bupropion *vs.* placebo [59].

Varenicline

Pharmacology and clinical pharmacology of varenicline

Varenicline is the most recently approved treatment for smoking cessation. Varenicline binds the α4β2 subtype nAChR with subnanomolar affinity and high selectivity. The affinity of varenicline for the α4β2 receptor is approximately three-fold and 16-fold greater than that of cytisine and nicotine (K_i of 0.06 nmol l^{-1}, 0.17 nmol l^{-1} and 0.95 nmol l^{-1}, respectively) [60, 61]. Varenicline is also a full agonist of homomericα7 nAChR [62]. It is hypothesized that varenicline has a dual mechanism of action: (i) it acts as a partial agonist at the α4β2 receptor that reduces the smoking cessation-induced drop in mesolimbic dopamine concentrations, potentially relieving withdrawal symptoms and (ii), consequent to its agonist activity and high affinity, it antagonizes the activity of nicotine at the α4β2 receptor and blocks nicotine-induced dopaminergic activation, potentially reducing the reward from smoking relapse [60, 63].

The plasma elimination half-life of varenicline is approximately 24 h. Because varenicline does not undergo significant hepatic metabolism, its pharmacokinetics are unaffected in patients with hepatic insufficiency. Varenicline is excreted in the urine, and its renal clearance is dose-proportional. In patients with mild renal impairment (creatinine clearance >50 ml min^{-1} and ≤80 ml min^{-1}), pharmacokinetics are unchanged compared with subjects with normal renal function. In patients with moderate renal impairment (creatinine clearance ≥30 ml min^{-1} and ≤50 ml min^{-1}), varenicline exposure is increased 1.5-fold. Similarly, varenicline exposure increases 2.1-fold in patients with severe renal impairment (creatinine clearance <30 ml min^{-1}). Therefore, caution is warranted with the use of varenicline in subjects with renal impairment, and when renal impairment is severe, dose adjustment is necessary [60].

Therapeutic efficacy of varenicline

The recommended dosage is 1 mg twice daily following a 1 week up-titration. However, it has been shown that a self-regulated, flexible dosing regimen of varenicline is well tolerated, with superior effectiveness *vs.* placebo [64]. Smokers treated with varenicline should normally aim to quit approximately 1 week after the start of the treatment. It has been shown, however, that using a flexible quit-date paradigm had efficacy and safety similar to those in the previous fixed quit-date paradigm [65]. Meta-analyses have confirmed the increased efficacy of varenicline on smoking quit rates at the dosage of 2 mg day^{-1} during a 12 week treatment compared with placebo and also to bupropion (see Table 1) [3, 66, 67]. For instance, the Cochrane review has shown a risk ratio over placebo of 2.27 (95% CI 2.02, 2.55). Only two published studies have compared varenicline with NRT [68, 69]. In an open but randomized study, varenicline performed better than the transdermal nicotine patch [68]. Varenicline has been shown to result in higher abstinence rates than combined or high dose NRT in some [35], but not all [1], meta-analyses. A 12 week treatment extension yields better cessation rates for smokers who quit successfully for at least 1 week at the end of the first 12 weeks of treatment [70]. The combination of varenicline with NRT or bupropion seems to be safe [71, 72], but no published, randomized controlled data exist as to the superiority of this co-administration over one or the other alone.

Like NRT and bupropion, varenicline has been shown to limit post-cessation weight gain during the active treatment phase, an effect that does not persist after treatment has ended [43]. In addition, some data suggest that varenicline may help reduce alcohol consumption in smokers who drink heavily [73, 74].

Safety and tolerability of varenicline

Phase I reports have shown that varenicline is tolerated after single doses up to 3 mg in smokers and 1 mg in non-smokers. Nausea and vomiting at doses above 3.0 mg in smokers and 1 mg in non-smokers are dose limiting [75]. Recent reviews of the safety profile of varenicline concluded that the most frequent adverse event was nausea, occurring in 30–40% of users [76–78]. The nausea was generally reported as mild to moderate and diminishing over time, and it was associated with low attributable discontinuation rates. Other common adverse effects included insomnia, abnormal dreams and headaches. In the randomized, controlled phase III studies, serious adverse events were rare, with no treatment-related deaths during the treatment or follow-up phases. There are currently no known contraindications to varenicline [79].

Post-marketing surveillance reports have suggested an increased risk of reported depression and suicidal/self-injurious behaviour with varenicline (and bupropion) compared with NRT [58, 80–82]. However, a pooled analysis of more than 5000 smokers without current psychiatric history who participated in one of 10 randomized, placebo-controlled clinical trials found that there was no significant increase in overall psychiatric adverse events aside from sleep disorders [83]. A study that assessed neuropsychiatric adverse effects failed to find any difference in measurements of depressive symptoms, anxiety, or aggression/

Table 2

Efficacy of combined pharmacotherapies for smoking cessation. U.S. Public Health Service clinical practice guideline meta-analysis

Combination therapies	Number of arms	Estimated OR (95% CI)
Nicotine patch (long term, >14 weeks) + ad lib NRT	3	3.6 (2.5, 5.2)
Nicotine patch + bupropion SR	3	2.5 (1.9, 3.4)
Nicotine patch + nortriptyline	2	2.3 (1.3, 4.2)
Nicotine patch + inhaler	2	2.2 (1.3, 3.6)

Adapted from The Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff [3]. CI, confidence interval; NRT, nicotine replacement therapy; OR, odds ratio; SR, sustained release.

hostility between varenicline and placebo among smokers without psychiatric disorders [84]. Furthermore, a retrospective analysis of 80 600 adults prescribed varenicline, using records from the UK General Practice Research Database, found that the incidence of depression and suicide was not greater with varenicline than with NRT or bupropion [85]. The post-marketing reports led the US Food and Drug Administration (FDA) and the European Medicine Agency to add a 'black box warning' to the product labelling for both varenicline and bupropion SR. Recently, two FDA-sponsored epidemiological studies that evaluated the risk of neuropsychiatric adverse events associated with smoking cessation drugs found no difference in risk of neuropsychiatric hospitalizations between varenicline and NRT [86]. Smoking and/or smoking cessation are frequently associated with neuropsychiatric symptoms and suicide-related outcomes [87]. Therefore, drug regulatory agencies acknowledge that distinguishing between drug-related adverse effects/events and the neuropsychiatric effects related to smoking and/or smoking cessation is difficult, and they strongly recommend that patients be closely monitored for neuropsychiatric symptoms [88].

A meta-analysis suggested an increased rate of cardiovascular events with varenicline [89]. However, a more recent meta-analysis that accounted for the major biases not taken into account in the previous work concluded that treatment with varenicline is not associated with increased rates of cardiovascular events compared with placebo [90].

Nortriptyline and clonidine have been proposed as second line pharmacotherapies by the US Clinical Practice Guidelines for treating tobacco use and dependence [1, 3].

Nortriptyline, a tricyclic antidepressant, is believed to block the re-uptake of norepinephrine and serotonin and, by this mechanism, reduce tobacco withdrawal symptoms [91]. Although nortriptyline has been confirmed as a smoking cessation drug (see Tables 1 and 2) [1, 3, 53], its unfavourable adverse effect profile prevented the drug from receiving FDA approval for smoking cessation. A well-powered, randomized, placebo-controlled study [92] and a meta-analysis [53] demonstrated that combining nortriptyline with NRT is no more effective than NRT alone.

Clonidine is an α_2-adrenergic agonist antihypertensive medication that decreases sympathetic outflow [32]. It is not approved for smoking cessation, but early studies demonstrated some efficacy, only among women, as an aid in smoking cessation (see Tables 1 and 2) [1, 3, 93]. Its unfavourable, dose-dependent adverse effect profile (dry mouth and sedation) and limited efficacy preclude its widespread use [93].

Special populations

Psychiatric comorbidity

Smoking prevalence among individuals with psychiatric disorders is 2- to 4-fold higher than in the general population [94], with even higher smoking prevalence rates among certain diagnostic groups, such as persons with bipolar disorder (60%) [95] or schizophrenia (65–90%) [96–98]. Individuals with a mental illness are also more likely to be heavy smokers [95] and to suffer more severe withdrawal symptoms [99]. Smoking may substantially increase cardiovascular morbidity and mortality among individuals with mental illness in association with atypical antipsychotics-induced weight increase and the consequent incidence of type 2 diabetes mellitus [100]. Despite increasing evidence that individuals with psychiatric disorders are motivated to quit [101], tobacco addiction remains an under-treated and under-recognized problem within this patient population [102].

The efficacy of NRT seems to be modest in smokers with schizophrenia, but abstinence rates seems to be higher among schizophrenics treated with NRT in combination with atypical antipsychotics compared with standard antipsychotics [103]. A recent meta-analysis showed that bupropion increased the rate of smoking abstinence in smokers with schizophrenia (RR = 2.78, 95% CI 1.02, 7.58) without jeopardizing their mental state [104]. Accumulating evidence shows that varenicline is also effective and safe in schizophrenic patients [105–110].

Several studies suggest that pharmacological treatments for tobacco addiction used in the general population can be similarly effective among those with depressive comorbidity. A secondary analysis of a smoking cessation study demonstrated that the smoking cessation rate among smokers with depression who used nicotine gum was more than twice the rate among those who used placebo gum [111]. However, to our knowledge, no specific study has assessed the efficacy of NRT in smokers with major depression. A meta-analysis of bupropion SR and nortriptyline found that these treatments are effective in increasing long-term cessation rates in smokers with a history of depression (OR = 3.42, 95% CI 1.70, 6.84) [1]. Assumptions that all antidepressants have comparable

effects owing to certain similarities in mechanisms of action have proven to be incorrect. Although both bupropion and nortriptyline are effective for smoking cessation, several studies have shown that selective serotonin re-uptake inhibitors do not increase abstinence rates [53].

Finally, the US clinical guideline for treating tobacco use and dependence recommends that smokers with psychiatric or addictive comorbidity use any medication proven effective in the general population of smokers, except when use of the medication is contraindicated [1].

Pregnancy

In addition to increasing pregnancy and perinatal hazards, maternal smoking during pregnancy is an independent risk factor for obesity, type 2 diabetes mellitus, smoking and tobacco addiction, and psychiatric disorders, all of which cause mortality up to age 20 years in the offspring [112]. Despite the risks associated with smoking during pregnancy, the number of pregnant women who smoke until delivery remains high. For example, it has been reported that during pregnancy 13% of women smoke in the US [113] and 18% of women in France [114]. NRT use during pregnancy is approved in some countries but not in others [115]. The use of NRT during pregnancy is controversial because nicotine has been shown to have foetotoxicity in animal models. In addition, previous randomized controlled trials have been inconclusive with respect to the efficacy and safety of NRT on cessation rates among pregnant smokers [113]. A very recent, sufficiently powered, randomized, placebo-controlled trial with a maximum of 2 months of nicotine patch exposure during the entire pregnancy did not find either an increased abstinence rate or higher birth weight with the nicotine patch as compared with a placebo patch [116]. Similarly, there was no difference in safety [116]. Because of the lack of randomized, sufficiently powered, controlled studies among pregnant smokers, neither bupropion nor varenicline is indicated for smoking cessation during pregnancy.

Adolescents

Given that that early smoking initiation is strongly associated with premature death [117] and that more than 80% of dependent smokers start smoking before the age of 18 years, tobacco addiction can be regarded as a youth disorder extending into adulthood [118]. Unfortunately, the burden of the disease does not always wait until midlife to manifest. For instance, smoking has been shown to independently predict suicide in adolescents and young adults [119]. A recent meta-analysis and systematic review detected no significant efficacy of pharmacological therapy in adolescents [120, 121]. Consequently, no definitive recommendations can be made regarding the use of pharmacotherapy for smoking cessation in this population of smokers, who are future candidates for smoking-related illnesses [1].

Pipeline developments

New galenic formulations of varenicline under development include a controlled-release formulation (Clinical Trials.gov Identifiers: NCT00741884 andNCT005227150), a free base patch (ClinicalTrials.gov Identifiers: NCT00741884, NCT01234142 and NCT01013454) and a free base solution (ClinicalTrials.gov Identifier: NCT00774605). The $\alpha 4\beta 2$ nAchR partial agonist cytisine has been used for decades as a smoking cessation drug in Eastern European countries and has been shown to be effective and safe as an aid for smoking cessation [122–125]. Other $\alpha 4\beta 2$nAchR partial agonists have been tested, with little success [126].

The finding that cigarette smoking is associated with inhibition of both monoamine oxidase (MAO) A and B subtypes has led to the hypothesis that MAO subtype-selective inhibitors may represent a novel class of medications that could be developed for smoking cessation [127–129]. Although early trials were promising [130, 131], subsequent trials yielded disappointing results. Selective MAO B inhibitors, either alone [132, 133] or in association with the nicotine patch [134], did not sufficiently increase the abstinence rate in powered, randomized, placebo-controlled trials.

Nicotine vaccines are designed to stimulate to the production of antibodies by the immune system that bind to nicotine in the bloodstream and prevent it from entering the brain by crossing the blood–brain barrier. With a reduced amount of nicotine reaching the brain, it is anticipated that the reinforcing effects of nicotine are diminished, thereby making it easier to quit smoking [135]. Three anti-nicotine vaccines are currently in advanced stages of clinical evaluation [136], including phase III (Clinical Trials.gov Identifiers: NCT01178346, NCT001102114). None of the vaccine studies carried out to date has reported major side effects [136]. Optimism has steeply decreased with the announcement that the vaccines did not increase abstinence rate in two of the phase III trials [137].

Medications that affect GABA or NMDA neurotransmission may decrease the reinforcing properties of nicotine, and thus may be useful as pharmacological treatments of tobacco addiction [28, 138]. Topiramate inhibits glutamatergic neurotransmission while simultaneously enhancing GABAergic tone [139]. Topiramate has been shown to produce gender-specific effects on smoking cessation. In a randomized placebo-controlled trial, men (but not women) were approximately four times more likely to quit smoking when treated with topiramate as compared with placebo [140]. Topiramate has also been shown to be effective in reducing smoking in alcoholic smokers [141, 142]. This drug has currently entered phase III of its development as an aid for smoking cessation (ClinicalTrials.gov Identifiers: NCT00755716 and NCT00280839). Baclofen, a selective GABA-B agonist, has shown some clinical and preclinical evidence for treating tobacco addiction [28]. A recent randomized placebo-controlled pilot trial

demonstrated a significant reduction in craving and smoking [143], and another randomized placebo-controlled trial is underway (ClinicalTrials.gov Identifier: NCT01228994). Two small scale trials have shown little promise of gabapentin treating smoking cessation [144–146]. Three drugs affecting NMDA are currently being investigated in phase I trials: memantine (ClinicalTrials.gov Identifier: NCT00136786), GW468816 [147] and cycloserine (ClinicalTrials.gov Identifier: NCT01062932). Finally, a pilot study exploring the effect of N-acetylcysteine has shown promising trends [148].

Modafinil is marketed as a wakefulness-promoting agent for excessive sleepiness associated with narcolepsy, obstructive sleep apnoea, and shift work sleep disorder [149]. Because of its efficacy in cocaine dependence [150] and its potential to alleviate nicotine/tobacco withdrawal symptoms [151], modafinil has been investigated as a treatment for smoking cessation [152]. However, the trial has been discontinued owing to the detrimental effect of the drug on smoking cessation. Dopamine D_3-receptor antagonists have shown promise in animal models [153]. GSK598809, a selective D3 antagonist, is currently being investigated in a phase II randomized placebo-controlled trial (ClinicalTrials.gov Identifier: NCT01188967).

Relapse prevention

Although behavioural support, nicotine replacement therapy, bupropion, and varenicline are all effective smoking cessation treatments, many smokers who stop after using these treatments subsequently relapse to smoking [154]. Consequently, any interventions that reduce relapse rates among abstinent smokers could have a substantial impact on maintaining long term abstinence [155]. Two recent meta-analyses propose different conclusions as a result of the different types of analysis performed [155, 156]. The Cochrane review concludes that extended treatment with varenicline may prevent relapse, that extended treatment with bupropion is unlikely to have a clinically important effect, and that studies of extended treatment with nicotine replacement are needed [156]. By contrast, the review by Agboola *et al*. concludes that all three medications, NRT, bupropion and varenicline, are effective in preventing relapse following an initial period of abstinence [155].

Conclusion

This review confirms that effective first and second line medications help smokers to quit. These treatments are effective across a broad range of populations, and clinicians should encourage and offer counselling and prescribe pharmacotherapy to any patient willing to attempt quitting. Some critics have suggested that smoking cessation medications have no useful applications in 'real-world' settings. However, systematic biases in cross-sectional community studies are likely to underestimate the effectiveness of smoking cessation medications [157].

Despite the relative efficacy of these treatments, many smokers relapse after a quit attempt, and alternative pharmacotherapies are needed [158] to increase cessation rates and to prevent relapses.

It is conceivable that tobacco use and addiction necessitate long term pharmacological treatments not only to induce abstinence but also to maintain it. If this is true, treatments that maintain long term smoking cessation and abstinence would contribute to the reduction of smoking-related morbidity and mortality. Because smoking is the main cause of premature death, morbidity-mortality studies related to smoking cessation medications should be implemented in the future.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, HJA and IB had a board membership, received payment for lectures including service on speakers bureau with Pfizer in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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