Pharmacotherapies and harm-reduction options for the treatment of tobacco dependence

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Introduction: Tobacco dependence, a chronic relapsing condition, requires repeated interventions and multiple attempts to quit.

Areas covered: Strategies for assisting smoking cessation include behavioural counselling and pharmacotherapy. Three drugs are currently used as first-line pharmacotherapy: nicotine replacement therapy (NRT), bupropion and varenicline. Compared to placebo, the drug effect varies from RR = 2.27 for varenicline, to 1.69 for bupropion, and 1.60 for any form of NRT. Cytisine (similar to varenicline) has a RR = 3.98 compared to placebo (two trials). Second-line pharmacotherapies include nortriptyline and clonidine. This review also offers an overview of pipeline developments.

Expert opinion: Effective medications exist, and clinicians should encourage and offer treatment to every smoker. However, most smokers try to quit by themselves, with only about 3% quitting successfully each year. Alternative interventions are needed. Harm reduction has not received much support to date. Safer alternative to tobacco smoking (smoke-free products, long-term use of cessation drugs, or electronic cigarettes) could save lives and reduce the burden of tobacco-related deaths and diseases. Despite some encouragement to develop a research agenda for e-cigarettes, particularly on the safety issues, too little attention has been brought to this area of research.

Keywords: bupropion, electronic cigarette, harm reduction, nicotine, nicotine replacement therapy, smokeless tobacco, smoking cessation, tobacco dependence, varenicline

1. Introduction

Tobacco dependence is classified as a chronic relapsing mental disorder [1,2] that for most users entails a struggle to achieve long-term abstinence. Tobacco dependence is responsible for > 5 million deaths worldwide each year, with an additional 600,000 people dying from second-hand smoke, and many of these deaths occur prematurely [3]. It is predicted that smoking will be responsible for approximately 1 billion tobacco-related deaths during the 21st century [4]. Quitting early in life (before 35) reduces by > 90% the overall risk of morbidity and mortality, both in men and women, but quitting at any age is beneficial [5,6]. Article 14 of the Framework Convention on Tobacco Control states that every country should implement and provide smoking cessation assistance [7]. Effective treatments (including behavioural counselling and pharmacotherapies) exist and are effective across a broad range of populations. It is therefore important that clinicians encourage and offer treatment to every smoker. Despite the continuing debate over the legitimacy of using resources for individual smoking cessation instead of policy measures and interventions [8-11], the cost-effectiveness of smoking cessation programmes has been consistently confirmed [12-14].

The proportion of smokers using smoking cessation services is however very low. For example, in Great Britain, where national networks of cessation services
2. Current pharmacotherapies

Three classes of drugs are currently marketed as first-line pharmacotherapy for smoking cessation: nicotine replacement therapy, bupropion and varenicline. Meta-analyses of the efficacy of these treatments in different settings have been published by the U.S. Department of Health and Human Services [17] and the Cochrane collaboration group [18-20]. 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 [17]. Since all medications are assumed to have some risk in pregnancy, psychosocial interventions should be the first treatment option for smoking cessation during pregnancy [22]. Because efficacy and safety have not been established for any of the first-line medication, no definitive recommendations can be made regarding the use of pharmacotherapy for smoking cessation during pregnancy [17,22].

2.1 Nicotine replacement therapy

Although the potential role of substances found in tobacco or its smoke other than nicotine has not been ruled out – in particular it has been shown that tobacco smoke contains substances that inhibit monoamine oxidase A and B [23,24] – nicotine is considered to be the main tobacco compound that causes and sustains tobacco dependence [16]. Nicotine replacement therapy (NRT) was the first proven effective pharmacological treatment of tobacco dependence (nicotine gum launched in Switzerland in 1978) and remains a first-line pharmacotherapy in the management of nicotine withdrawal symptoms [25]. NRT makes it easier to abstain from smoking by replacing, at least partially, the nicotine formerly obtained from tobacco. NRT administration has been shown to reverse the nicotine withdrawal symptoms and cravings observed upon discontinuation of smoking [26]. Depending on the countries, NRT comes in some or all of the following formulations: gum, transdermal patch, nasal spray, sublingual tablet, lozenge, inhaler and mouth spray. They can be purchased over-the-counter in many countries, and are therefore the only non-prescription effective drugs for smoking cessation. Other nicotine delivery systems are currently being developed, among them the electronic cigarette has received great attention recently as it seems that its use is becoming very popular among smokers in many countries [27-29]. The multiple formulations of NRT offer smokers a choice in the route of administration, which may have a positive influence on adherence to treatment [30]. The transdermal patch system offers a continuous release of nicotine over 16 or 24 h depending on the brand, whereas the oral formulations are short-acting, so the dose can be self-titrated, and thus time-adjusted to the patients’ needs [30]. Thus oral NRT is thought to improve cessation efforts also through providing an alternative coping strategy at times when cravings may occur [31]. The absorption kinetics of nicotine are important when considering the psychological or subjective effects which also play a role in tobacco dependence. Blood nicotine concentration rises quickly during cigarette smoking and peaks at the completion of each cigarette smoking. Since absorption of nicotine is slower with NRT, it does not fully reproduce the positive subjective effects of smoked nicotine [32]. Despite these differences, NRT has shown to be effective in increasing quit rates with a significant risk ratio (RR) of abstinence for any form of NRT relative to placebo (117 clinical trials) of RR = 1.60 (95% confidence interval [CI] 1.53 – 1.68) [18]. The most recent formulation, the mouth spray (one clinical trial) has a RR = 2.48 (95% CI 1.24 – 4.94) compared to placebo [33]. Results from a clinical trial on urges to smoke suggest that nicotine mouth spray reduces craving faster than nicotine lozenge, which could confer to this new oral formulation an advantage that could translate in better outcomes [34]. There is evidence that combining the transdermal patch with an oral formulation improves the efficacy of NRT [18]. A recent meta-analysis has shown that NRT limits post-cessation weight gain during the active treatment phase [35]. NRT is usually started the day of...
the programmed quit date, but may also be used to assist smoking reduction in preparation for a quit attempt [36]. Pre- cessation treatment, usually 2 weeks before quit date, although estimated as safe, showed conflicting efficacy results in terms of abstinence, and just missed statistical significance in the recent Cochrane meta-analysis (RR = 1.18, 95% CI 0.98 – 1.40; eight clinical trials) [18]. NRT has an overall favourable safety profile, most adverse events are mild and transient. Transdermal patches can cause mild skin irritation and disturbed sleep; nicotine gum can cause jaw pain, mouth soreness, dyspepsia and hiccups; nicotine inhaler may lead to mouth and throat irritation and cough; nicotine lozenge and mouth spray can cause mouth and throat irritation and hiccups; and nicotine nasal spray may cause runny nose, throat and nasal irritation [30,33,37].

2.2 Bupropion

Sustained-release bupropion (bupropion SR) was the first non-nicotine treatment to demonstrate efficacy in smoking cessation (launched in the US in 1997), but was first approved as an atypical antidepressant. Bupropion SR has since been approved for smoking cessation in many other countries. Bupropion is blocking the reuptake of dopamine and noradrenaline in the mesolimbic system and the nucleus accumbens [38], but is also acting as an antagonist on nicotinic receptors and hence blocks to some extent the reinforcing effects of nicotine [39]. The efficacy of bupropion has been well established through several meta-analyses [17,19]. From the 36 clinical trials analysed by the Cochrane group, bupropion has been shown to significantly increased long-term cessation compared to placebo (RR = 1.69; 95% CI 1.53 – 1.85) [17]. Adding NRT to bupropion may provide an additional long-term benefit, however the evidence is insufficient (six trials, RR = 1.23; 95% CI 0.67 – 2.26) [17]. From the available data, bupropion appears to be of similar efficacy to nicotine replacement therapy, but less than varenicline (RR = 0.66, 95% CI 0.53 – 0.82) [17]. In addition to increasing quit rates, bupropion has also been shown to decrease nicotine withdrawal symptoms and cravings [40], to be as effective in women as in men for long-term abstinence and relapse prevention [41,42], and to reduce post-cessation weight gain, at least during the course of treatment [43]. Bupropion SR is generally well tolerated [44]. Adverse events associated with the use of bupropion SR at the recommended dosage of 150 mg twice daily in clinical trials most commonly included insomnia, headache, dry mouth, nausea and anxiety; insomnia and anxiety are also recognised as symptoms of nicotine withdrawal. Only insomnia and dry mouth occurred significantly more frequently with bupropion SR than with placebo, but are generally transient and often resolve quickly without therapeutic intervention, a reduction of the dose may be recommended when necessary. Infrequent but clinically important adverse reactions to bupropion SR include seizures and hypersensitivity reactions. Bupropion has been shown to be safe for patients with cardiovascular disease [45] or COPD [46]. 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 of alcohol or sedatives, because of an increased risk of seizures (lowered threshold). 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 to NRT [47]. However, a meta-analysis of controlled studies did not show any increase in suicidal behaviour with bupropion versus placebo [48].

2.3 Varenicline

Varenicline is the most recently approved treatment for smoking cessation (launched in the USA and UK in 2006). It is a partial agonist for the α4β2 subtype of nAChRs, which are associated with the addictive properties of nicotine [49]. Because of both agonist and antagonist properties of the drug on the α4β2 subtype of nAChRs, it decreases nicotine withdrawal and craving (a consequence of its agonist activity) and also decreases the reinforcing effect of smoking (a consequence of its antagonist activity). Varenicline is formulated as 0.5 and 1.0 mg tablets. The recommended dosage is 1 mg twice daily following a 1 week titration. However, it has been shown that a self-regulated, flexible dosing regimen (0.5 – 2.0 mg/day) of varenicline is well tolerated, with superior effectiveness versus placebo for smoking cessation [50]. The most recent meta-analysis (14 clinical trials) of varenicline efficacy for continuous or sustained abstinence at 6 months or longer at standard doses versus placebo gives a RR = 2.27 (95% CI 2.02 – 2.55) [20]. Varenicline used at lower or variable doses (four clinical trials) has also been shown to be effective, with a RR = 2.09 (95% CI 1.56 – 2.78). Varenicline presents a favourable RR at 1 year compared to bupropion, RR = 1.52 (95% CI 1.22 – 1.88), and a non-significant advantage over NRT for point prevalence abstinence at 24 weeks with RR = 1.13 (95% CI 0.94 – 1.35) [20,51]. A more recent report on data from 167,487 treatment episodes in England gives a small advantage to varenicline compared to combination NRT (patch + oral formulation), with an odds ratio of 1.080 (95% CI 1.003 – 1.063), and a difference in abstinence rate of 1.866% (95% CI 0.07 – 3.67%; p=0.04) [52]. Reviews of the safety profile of varenicline concluded that the most frequent adverse event (AE) was nausea, occurring in 30 – 40% of varenicline users [53,54]. However, this was generally reported as mild to moderate, diminished over time and was associated with low attributable discontinuation rates. Other commonly occurring AEs include insomnia, abnormal dreams and headache. Serious AEs were rare, with no

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treatment-related deaths during the treatment or follow-up phases. There are currently no known contraindications to varenicline therapy [55]. Varenicline has been administered concurrently with warfarin, digoxin, transdermal nicotine, bupropion, cimetidine and metformin without any clinically significant drug interactions [56]. Recently, there have been postmarketing reports of varenicline being associated with increased risk for depressed mood, as well as changes in behaviour, hostility, agitation, suicidal thoughts and behaviour and attempted suicide [53]. Similar incidents of suicidal thoughts and behaviour have been reported for bupropion SR and these postmarketing reports led to the US Food and Drug Administration (FDA) to add a ‘boxed warning’ to the product labelling for both varenicline and bupropion SR. The US FDA acknowledges, however, that distinguishing between drug-related AEs and the neuropsychiatric effects related to smoking cessation itself is a difficult challenge and it urges the close monitoring of patients for neuropsychiatric symptoms [56]. A pooled analysis of over 5000 smokers without a current psychiatric history who had participated in one of ten randomised, placebo-controlled clinical trials found that there was no significant increase in overall psychiatric AEs, except for sleep disorders and disturbances [57], and a retrospective analysis of the UK General Practice Research Database for 80,600 adults prescribed varenicline found that the incidence of depression and suicide were not greater for varenicline than for NRT or bupropion [58].

2.4 Other pharmacotherapies

Nortriptyline and clonidine have been proposed as second-line pharmacotherapies [17]. Nortriptyline, a tricyclic antidepressant, is believed to reduce tobacco withdrawal symptoms by blocking the re-uptake of noradrenaline and serotonin. Although nortriptyline has been confirmed as a smoking cessation drug [19], its unfavourable adverse effect profile prevented the drug from receiving approval for smoking cessation. A meta-analysis demonstrated that combining nortriptyline with NRT is no more effective than NRT alone [19].

Clonidine, an α2-adrenergic agonist, is an antihypertensive medication that decreases sympathetic outflow [30]. It is not approved for smoking cessation, but early studies demonstrated some efficacy, only among women, as an aid for smoking cessation [17,59]. Its unfavourable, dose-dependent adverse effect profile (dry mouth and sedation) and limited efficacy preclude its widespread use [59].

Cytisine, an α4β2 nAChR partial agonist similar to varenicline, 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 [20,60]. Two recent cytisine trials (937 people) found that more participants taking cytisine stopped smoking compared with placebo at longest follow-up, with a pooled RR = 3.98 (95% CI 2.01–7.87) [61,62]. Its low cost, compared to other pharmacotherapies for smoking cessation, may make it an affordable treatment for low income countries [61].

3. Future treatments

New galenic formulations of varenicline under development include a controlled-release formulation (ClinicalTrials.gov Identifiers: NCT00741884 and NCT005227150), a free base patch (ClinicalTrials.gov Identifiers: NCT00741884, NCT01234142 and NCT01013454), and a free base solution (ClinicalTrials.gov Identifier: NCT00774605). 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 [24]. Although early trials were promising [63,64], subsequent trials yielded disappointing results. Selective MAO B inhibitors, either alone [65,66] or in association with the nicotine patch [67], did not sufficiently increase the abstinence rate in powered, randomised, 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 [68]. However, none of the vaccine studies carried out to date has reported significant increased abstinence rate, and a recent trial of nicotine vaccine used in relapse prevention failed to show a significant effect, which conducted the producer to stop further development [69].

Medications that affect GABA or NMDA neurotransmission may decrease the reinforcing properties of nicotine, and thus may be useful as treatments of tobacco dependence [70]. Topiramate inhibits glutamatergic neurotransmission while simultaneously enhancing GABAergic tone [71]. In a randomised placebo-controlled trial, men (but not women) were approximately four times more likely to quit smoking when treated with topiramate as compared to placebo [72]. Topiramate has also been shown to be effective in reducing smoking in alcoholic smokers [73,74]. This drug has 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 dependence. A randomised placebo-controlled pilot trial demonstrated a significant reduction in craving and smoking [75], and another randomised placebo-controlled trial is ongoing (ClinicalTrials.gov Identifier: NCT01228994). Three drugs acting on NMDA receptors are currently being investigated in Phase I trials: memantine (ClinicalTrials.gov Identifier: NCT00136786), GW468816 [76] and cycloserine (ClinicalTrials.gov Identifier: NCT01062932). Finally, a pilot study exploring the effect of N-acetylcysteine has shown some promising effects [77].

Modafinil is marketed as a wakefulness-promoting agent for excessive sleepiness associated with narcolepsy, obstructive
sleep apnoea, and shift work sleep disorder [78]. Modafinil has been investigated as a treatment for smoking cessation, but the trial was discontinued owing to the detrimental effect of the drug on smoking cessation [79].

D3 receptor antagonists have shown promise in animal models [80]. GS998809, a selective D3 antagonist, is currently being investigated in a Phase II randomised placebo-controlled trial (ClinicalTrials.gov Identifier: NCT01188967).

4. Harm reduction

Tobacco harm reduction consists in reducing the net damage to health associated with the use of tobacco products. Models of harm reduction applied to tobacco suggest that the use of non-combustible, less toxic, nicotine containing products would be better than cigarette smoking in limiting the tobacco-related deaths and disabilities. Smoking, the most harmful and addicting form of tobacco use, usually starts in adolescence, and determination to quit peaks in general at middle age (around 35 – 50 years old). This can result in a successful quit attempt where harm can be reduced to that of a never-smoker depending on the age at which cessation occurs [5,6]. However, many smokers cannot or do not want to give up, and little effort has been put into reducing the harmfulness of their continued tobacco use. The sooner the action starts and the less hazardous the product is, the greater the harm reduction [81].

To date, tobacco control policy has mostly focused on reducing initiation in young people, and quitting in current smokers. Harm-reduction approaches have largely been focused on reducing the harmfulness of exposure to second-hand smoke. The tobacco industry has developed potentially reduced exposure products (PREPs) which deliver smoke containing lower levels of nitrosamines (cancer causing substances) or other toxins. However none of these products has been shown to reduce the health hazard of tobacco use, and it is unlikely that combustible products will ever present a significant harm-reduction profile. Conversely, switching smokers from inhalation of combustible products to a non-combustible nicotine delivery product would likely result in a vast reduction in tobacco-caused death and illness, via major reductions in lung cancer and chronic respiratory disorders [82]. Three products could be used for tobacco harm reduction: smokeless tobacco, NRT and electronic cigarettes. Smokeless tobacco products are not a homogeneous category and the risk profile varies according to the products, but data from Sweden, where a large percentage of young men use snus (a snuff product with reduced amount of nitrosamines) and the prevalence of smoking is lower than in other European countries, show markedly lower rates of lung cancer compared with populations in other countries. Moreover, observational studies have also found that snus is used by many smokers to quit smoking [83]. However, currently, supplying snus is illegal in EU countries other than Sweden. NRT is generally regarded as safe other than when used in pregnancy where the evidence is limited.

Although there is little evidence on long-term use of NRT, it is thought to be unlikely that there would be major long-term adverse effects on health, and certainly not in relation to the hazards of smoking. NRT products currently available have achieved only partial success with regard to these issues, because they provide nicotine at doses and rates of delivery that are a poor substitute for cigarettes. In addition, NRT products are available through fewer retail outlets than cigarettes, and their medicinal packaging and pricing means that they are less appealing to tobacco users than cigarettes. The regulation of NRT has recently been changed, and is more relaxed in some countries (e.g., France, UK), but if we want NRT to compete against tobacco efficiently we need to improve this situation and make NRT much more accessible, and much more affordable than cigarettes. It is also important to encourage the development of more effective NRTs. The ideal option, aside from quitting all nicotine use, would be for smokers to switch from cigarettes to a “clean addictive nicotine delivery system” [84]. This could be the case with the new nicotine delivery device that is now gaining increasing support from smokers; the electronic cigarette. In many countries, the electronic cigarette is currently considered as a consumer product and is available from internet or specialised shops. But its regulatory status is scrutinised by many authorities, and the proposed updated Tobacco Products Directive of the European Commission is considering to regulate them as medicinal devices [85]. This could be seen as a way to ensure consumer safety, but could also halt the development of these new products because it would result in increasing substantially the price and make it less attractive compared to cigarettes. Finally, there is a concern that the availability of lower hazard nicotine delivery products may lead to use among people who would not otherwise have used a tobacco product. At low levels of hazard, any public health impact from this is likely to be more than offset if substantial numbers of smokers switch to a lower hazard product [86]. However, there is disagreement, for example, on the extent to which snus has contributed to declining smoking prevalence in Sweden, and whether this experience and the balance of harm to benefit to society arising from the availability of snus could be replicated in other countries [84]. The data currently gathered worldwide about e-cigarette use may help to shed some light on these issues.

5. Conclusion

Despite the fact that we dispose of effective treatments, and that quitting early in life reduces most of the risk of morbidity and mortality, tobacco smoking is still the first avoidable cause of death and disabilities all over the world. The three current first-line treatments (NRT, bupropion and varenicline) are effective and clinicians should encourage and offer treatment to every smoker. Unfortunately, this is not what is observed at the population level in many countries. Most smokers try to quit by themselves, which is the least effective
method. Even if every year about 40% do quit for at least 1 day, approximately 80% of smokers who attempt to quit on their own return to smoking within a month, and only 3% of smokers quit successfully each year. Tobacco harm reduction, which aimed at reducing the harm caused by tobacco smoking in continuing smokers, has been overlooked so far by the smoking cessation and tobacco control communities. Nevertheless, effective alternative to tobacco smoking, the most addictive and deadly form of tobacco use, do exist, and snus use in Sweden, or the new electronic cigarette used by an increasing number of smokers all over the world, are examples of harm-reduction approaches that could help reduce substantially tobacco death toll in the near future [87].

6. Expert opinion

Tobacco dependence is responsible for > 5 million deaths worldwide each year, and many of these deaths occur prematurely [3]. Tobacco dependence killed 100 million people in the 20th century, and it is predicted that it will be responsible for approximately 1 billion deaths during the 21st century [4]. Quitting early in life (before 35) reduces by > 90% the overall risk of morbidity and mortality, both in men and women, but quitting at any age is beneficial [5,6]. Effective medications exist and the smoking cessation field is fortunate enough to dispose of three effective first-line medications, and two second-line drugs. These treatments are effective across a broad range of populations, and clinicians should encourage and offer treatment to every smoker [88,89]. Unfortunately, this is not what is observed at the population level in many countries. Despite the relative efficacy of these treatments, most smokers try to quit by themselves, which is the least effective method, and approximately 80% return to smoking within a month, with only about 3% quitting successfully each year [16]. Consequently, alternative pharmacotherapies or interventions are needed. One particular intervention, harm reduction, has not received much support from the smoking cessation and tobacco control communities. Safer alternative to tobacco smoking (smoke-free products, long-term use of NRT, or electronic cigarettes) could save lives and reduce the burden of tobacco-related deaths and diseases. Following the apparition of the electronic cigarette and the rate at which it seems to infiltrate the population of smokers, we are probably experiencing a revolution in the domain of smoking cessation and tobacco control. For the first time in history (at the exception of snus in Sweden), a new product seems to be able to compete with cigarettes. The speed at which e-cigarettes spread all over the world may have soon more impact than current interventions, and may actually be more effective in reducing drastically the prevalence of tobacco use and tobacco-related deaths, particularly in countries where prevalence is staging [87]. Despite some encouragement to develop a research agenda in this domain, too little attention has been brought to this area of research [90]. These new nicotine delivery devices may also prove a perfect vehicle to administer nicotine in non-smokers to treat psychiatric and neurological conditions [91], and eventually to administer other drugs than nicotine (e.g., antibiotics, asthma medications) [90].

Declaration of interest

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Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.

Pharmacotherapies and harm-reduction options for the treatment of tobacco dependence


* This paper is crucial to underscore the need to invest in tobacco dependence treatments.


** An important review on the mechanisms of tobacco dependence.


* An important study on e-cigarettes’ users.


* An important study on e-cigarettes’ users.


* A paper highlighting the role of the speed of absorption of nicotine in the dependence process.

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