New Pharmacological Agents to Aid Smoking Cessation and Tobacco Harm Reduction: What has been Investigated and What is in the Pipeline?

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Abstract

A wide range of support is available to help smokers to quit and aid attempts at harm reduction, including three first-line smoking cessation medications: nicotine replacement therapy, varenicline and bupropion. Despite the efficacy of these, there is a continual need to diversify the range of medications so that the needs of tobacco users are met. This paper compares the first-line smoking cessation medications to: 1) two variants of these existing products: new galenic formulations of varenicline and novel nicotine delivery devices; and 2) twenty-four alternative products: cytisine (novel outside of central and eastern Europe), nortriptyline, other tricyclic antidepressants, electronic cigarettes, clonidine (an anxiolytic), other anxiolytics (e.g. buspirone), selective 5-hydroxytryptamine (5-HT) reuptake inhibitors, supplements (e.g. St John's wort), silver acetate, nicobrevin, modafinil, venlafaxine, monoamine oxidase inhibitors (MAOI), opioid antagonist, nicotinic acetylcholine receptors (nAChR) antagonists, glucose tablets, selective cannabinoid type 1 receptor antagonists, nicotine vaccines, drugs that affect gamma-aminobutyric acid (GABA) transmission, drugs that affect N-methyl-D-aspartate receptors (NMDA), dopamine agonists (e.g. levodopa), pioglitazone (Actos; OMS405), noradrenaline reuptake inhibitors, and the weight management drug lorcaserin. Six criteria are used: relative <u>e</u>fficacy, relative <u>s</u>afety, relative <u>c</u>ost, relative <u>u</u>se (overall impact of effective medication use), relative <u>s</u>cope (ability to serve new groups of patients), and relative <u>e</u>ase of use (ESCUSE). Many of these products are in the early stages of clinical trials, however, cytisine looks most promising in having established efficacy and safety and being of low cost. Electronic cigarettes have become very popular, appear to be efficacious and are safer than smoking, but issues of continued dependence and possible harms need to be considered.

Key points:

- This paper reviews 26 pharmacotherapies that have been investigated for tobacco harm reduction and smoking cessation alongside three first-line treatments (nicotine replacement therapy, varenicline and bupropion) on six criteria: relative efficacy, relative safety, relative cost, relative use, relative scope, and relative ease of use.

- Although many of these products are in the early stages of clinical trials, of all the medications considered, cytisine appears to offers the best prospect for the future, having established safety and efficacy and being very inexpensive. Electronic cigarettes have become very popular in some countries but efficacy and long-term safety compared with other treatment profiles require further consideration.

1. Introduction

Despite significant declines in the prevalence of tobacco use in many countries over the past couple of decades [1], smoking remains the leading avoidable cause of premature death worldwide, accounting for more than 5 million deaths per year [2]. Smoking is also responsible for multiple morbidities including cancer, heart disease, stroke, emphysema, bronchitis, chronic airway obstruction, and diabetes [3].

Bupropion, nicotine replacement therapy (NRT), and varenicline are licensed as first-line smoking cessation aids in Australia, the European Union, and North America, and are recommended in many national guidelines [4]. There is substantial evidence from clinical trials, population studies, and routine clinic data for the efficacy of these medications for cessation, and the use of NRT for harm reduction [5-10].

Yet, some smokers find these three traditional medications unacceptable [11] and in many countries they are not affordable [12]. This paper aims to review alternative medications which have been assessed for smoking cessation and harm reduction alongside the three first-line products using six criteria that we propose (ESCUSE): relative efficacy, relative safety, relative cost, relative use (overall impact of effective medication use), relative scope (ability to serve new groups of patients), and relative ease of use.

1.1 ESCUSE criteria

1.1.1 Relative efficacy: Is the product more efficacious than existing drugs?

Efficacy is the extent to which an intervention does more good than harm under ideal circumstances (usually a clinical trial) i.e. does the drug work? We are often interested in whether novel treatments have greater or similar efficacy to established pharmacotherapy. However, efficacy is often hard to address for novel treatments due to the absence of long-term clinical trials. Indeed, up to 97% of data on the efficacy of medication is based on short term surrogate end-points [13]; and even where high quality clinical data are available, medicines sometimes do not perform as expected in everyday clinical practice [14]. This is because effectiveness – the ability of a drug to produce a beneficial effect in real-world settings – is highly dependent on compliance with the drug routine. However, the effect of delivery in routine clinical settings is generally only possible to assess once a drug is licensed for its indication. Consequently, where information on efficacy and effectiveness are unavailable, we will draw conclusions from research on other drugs with similar pharmacotherapy profiles. For example, both cytisine and varenicline act as nicotinic receptor partial agonists, while NRT and electronic

cigarettes are based on the principle of providing pure nicotine without the toxic constituents of tobacco.

1.1.2 Relative **s**afety: Is the product safer than existing drugs?

The safety profile of a drug is often viewed as a top priority in evaluating the possible public health impact of a novel treatment. A product which is equally effective as an existing product, but deemed less dangerous, will likely have an overall public health benefit; while a product which is equally effective, but deemed more dangerous, may have a negative public health impact [15]. Side effects can range from being mild and short-lived to being severe and long-lasting, the latter needing to be minimised or ideally removed in products coming to market. Generally, evidence for the safety profile of a drug comes from clinical trials and population surveillance. However, as a number of novel treatments have not been evaluated long-term, safety assurances necessarily rely on expert judgment and pharmacological profiles, and should be updated regularly as new information emerges. For instance, research in the US shows that post-marketing surveillance generally only identifies serious drug reactions a median of three years after approval [16].

1.1.3 Relative **c**ost: Is the product cheaper than existing drugs?

The cost of a new drug should always be considered in the overall assessment of its place in the treatment of dependence. Around the world, health-care service budgets are increasingly under strain, and thus drugs which are deemed effective may only be available if they come at a suitable cost. Indeed, cost-effectiveness is viewed as the 'fourth hurdle' among the criteria of drug regulation and licensing decisions, given that the cost of new drugs is nearly always significantly higher than the drugs they aim to replace [17].

1.1.4 Relative **u**se: Will the product increase the number of patients using some form of effective medication?

Increased public health benefits at a population level from new treatments will occur either when: 1) smokers switch to a more effective novel product; or 2) the novel product entices smokers not using pharmacotherapy to use effective medication. Thus, there is a need to assess whether the presence of the drug in the market will increase the overall use of pharmacotherapy. Prior to the drug's availability, informed hypotheses can be made but it is not possible to ascertain its true impact. Even once the drug is in use at a population level, long-term surveillance will be required since initial effects may not be maintained [18].

1.1.5 Relative **s**cope: Does the product serve groups of patients who are not adequately served by existing drugs?

Often the aim of novel treatments is to serve a group of patients who are not adequately served by existing medications. Medications regularly have contraindications for at-risk populations and are not equally available in all countries. For example, patients who are pregnant, suffer from cardiovascular disease, and/or have psychiatric conditions, are often warned against condition-unrelated-pharmacotherapy due to the possibility of adverse effects. Novel treatments can also be required to meet individual preferences for the delivery method, the potency and action of a drug [11, 19]. There have been increasing moves towards the personalisation and stratification of treatment, including 'mutually agreed tailoring', which involves the management of conditions by incorporating specific needs and experiences with clinical judgement to decide on drug routines [20-23].

1.1.6 Relative **e**ase: Is the product easier to take than existing drugs?

Less than half of all drugs are taken as recommended [24]. Consequently, simplifying a drug routine can be an important step in promoting adherence. Simplification can involve reducing dose complexity (e.g. from four times a day to once a day), changing the mode of delivery (e.g. from injection to tablet) and helping patients to integrate the regimen into their daily lives [24].

2. First-line treatments for smoking cessation and harm reduction

NRT was introduced in 1978 in Switzerland as a chewing gum formulation (Canada in 1979 and UK in 1980) followed by the nicotine patch in the US in 1992 [25]. The basis of the development of NRT was evidence that the main addictive component of cigarettes is nicotine [26-28], but that it is the other thousands of chemicals resulting from cigarette combustion that cause the excess mortality and morbidity [29, 30]. The market over the next 30 years expanded rapidly, with the development of faster acting products such as the nicotine inhalator, nicotine lozenges, nicotine nasal spray, fast dissolving oral nicotine strip and nicotine mouth spray [31, 32]. Variations also became available in a number of counties including high strength patches [33], rapid delivery gums [34] and mini lozenges which dissolve more quickly than the standard lozenge [35]. These products were initially only licensed for smoking cessation but have subsequently been recommended in a number of countries, including the UK, for harm reduction [36].

The next first-line treatment introduced to market was bupropion. This atypical antidepressant was proposed as a smoking cessation aid by Ferry in 1989 following the observation that smokers taking it for depression stopped smoking spontaneously [37]. However, it was not approved as a smoking cessation aid until 1997, after a series of manufacturer funded clinical trials [37]. Bupropion, marketed

under its trade name Zyban and Wellbutrin, is thought to help smokers to quit through its ability to inhibit the neuronal reuptake of dopamine, noradrenaline (norepinephrine) and serotonin/5-hydroxytryptamine (5-HT) [38].

The third first-line treatment varenicline (Chantix, Champix), a nicotinic acetylcholine receptor (nAChR) partial agonist and synthetic derivative of the alkaloid cytisine, entered the UK and US markets in 2006 [39, 40]. It was hypothesised that a partial agonist of nAChRs would lead to a moderate and sustained increase of mesolimbic dopamine levels, thus reducing withdrawal symptoms. At the same time, varenicline was argued to shield a smoker from dependence-maintaining increases in neurotransmitters due to its higher affinity to nAChRs than the native ligand, nicotine, and therefore reduce the rewarding effects of smoked tobacco [41].

Table 1 applies the ESCUSE criteria to these three first-line treatments and forms the baseline for comparing novel pharmacotherapies. Varenicline appears to be the most effective of the three medications, but has the greatest number of apparent side effects and contraindications. NRT offers smokers greater variety and is substantially cheaper but often is not adhered to or used correctly, while bupropion may be a suitable treatment for individuals with co-morbid depression diagnoses but is also associated with increased seizure risk.

3. Other pharmacotherapy for smoking cessation and harm reduction

Over the past couple of decades attempts have been made to devise alternative novel pharmacotherapies based either on the first-line treatments or drugs which work via alternative mechanisms. These products are reviewed below, starting with variants of existing products and then products with novel mechanisms, in order of their likely efficacy.

3.1 Variants of Existing Products

3.1.1 Novel nicotine delivery products

Promoted by the unpleasant taste and side effects of traditional NRT products [42, 43], a number of alternative devices have been proposed. These included the nicotine straw, a single use straw which contains small beads and drops of nicotine [44]; nicotine pouches, which contain flavoured nicotine granules [45]; pulmonary nicotine delivery devices, which deliver nicotine into the lungs in the form of nebulisers, pressurised metered-dose inhalers and other non-metered-dose inhalers [46]; carbon nanotubes which are transdermal and have gate-keeping properties [47]; the Nicotine Cannon, a wide-bore nicotine delivery device which holds up to five inhalator cartridges [48]; and other nicotine films which attempt to combine the properties of both oral and transdermal products i.e. increased speed of nicotine delivery, flexibility in application and bi-phasic nicotine release [49]. Most remain in early

stages of development, with the exception of the nicotine pouch which is available in some countries, including Sweden, while work on the nicotine straw has become dormant for unknown reasons [32].

Relative efficacy

Although there is currently limited evidence for the efficacy of these novel nicotine delivery devices in relation to smoking cessation, preliminary data suggests that they may be as effective as or more effective than licensed NRT in reducing withdrawal symptoms and desire for cigarettes [32]. Some of the products deliver nicotine as fast or faster than licensed NRT and are judged to be more enjoyable and satisfying to use. In a repeated measures crossover trial the nicotine cannon alleviated urges to smoke and was deemed to be more acceptable by users, while a small randomised trial of twenty-four smokers found that plasma levels of nicotine peaked between 1 and 2 hr after a single dose, which is comparable with that of other nicotine replacement products [44, 50]. However, the nicotine straw is likely to be ineffective when used in combination with beverages with lower pH values [43]. Nebulisers and nicotinic inhalers have also been shown to reduce the desire for cigarettes [46, 51]. Carbon nanotubes through their ability to control flow of nicotine across the membrane may over-come many of the limitations of the traditional patches, allowing programmable variable drug delivery rates [52].

Relative safety

Devices that deliver nicotine through the bronchial alveoli, as is achieved by cigarettes, may have greater abuse potential [44]. Although many of the products, including the nicotine straw, are well tolerated [53]; they have mild side effects, particularly the pulmonary delivery devices which are aversive at high doses [50]. A recent systematic review reported that nebulizers elicit dose-dependent coughs [54]. Dose-dependent reflux interruption of smooth inspiration has also been reported for metered-dose inhalers in clinical trials [54]. However, some novel products may have more favourable side effects than established NRT, which can cause hiccups, nausea and local irritation.

Relative cost

Although adaptations of an existing product has the advantage of being potentially cheaper and easier to produce and license than the other treatments discussed below, some of these products may be more expensive (e.g. the nicotine cannon which requires multiple inhalator cartridges) [41].

Relative use

None of the products, with the exception of nicotine pouches, are currently available to smokers. However, if they were to be licensed it is likely that they will increase overall use of non-tobacco nicotine containing products, based on evidence that bringing new nicotine delivery devices into the

market results in more smokers trying pharmacological aids [55]. Previous studies suggest that novel products do not simply substitute for existing ones [56, 57].

Relative scope

These products may be particularly suitable for those who find traditional NRT products ineffective or unacceptable [58]. However, they are likely to be contraindicated for similar populations as traditional NRT products and may, in the case of pulmonary delivery devices, have a greater number of side effects.

Relative ease of use

Use of these nicotine delivery devices is similar to traditional NRT products. For example, the nicotine cannon 50mg (5 x 10mg cartridges) and pulmonary delivery devices can be used as needed, while nicotine straws in 4, 8 or 12 mg can be used every 1-2 hours.

3.1.2 New galenic formulations of varenicline

Galenic formulations of varenicline have been considered in order to improve the efficacy and acceptability of the traditional varenicline formulation. Galenic formulation is the process of medication preparation and compounding in order to optimise both the rate and extent of medication absorption. To date three new galenic formulations of varenicline have been proposed and are currently being tested in randomised controlled trials.

The first is a free base patch which aims to deliver varenicline transdermally. Four phase 1 clinical trials assessing absorption rates and tolerability have been completed (Clinical trial identifier and completion date: NCT01234142 in 2011 and NCT01013454 in 2009, NCT00661765 in 2009 and NCT00774605 in 2009).

The second is a controlled-release tablet formulation. This aims to slow the rate of release of varenicline in the gastro-intestinal tract and extend the absorption phase [59]. This has been achieved using an osmotic controlled-release system, where a tablet core made from varenicline, mannitol, microcrystalline cellulose, and dicalcium phosphate, and is coated with a porous and semipermeable coating. As water enters the coating and the core, the drug is dissolved and released into the blood stream [60]. Two clinical trials have been completed which assessed the absorption rate, pharmacokinetics, safety and tolerability of single dose and escalating multiple oral doses of varenicline controlled-release tablets (NCT00731562 in 2010 and NCT00527150 in 2010). A further clinical trial, which planned to evaluate the safety and efficacy of three doses of controlled-release

varenicline specifically for smoking cessation, was terminated prior to participant enrolment (NCT00741884).

The third is a free base solution which can be applied to the skin in the form of an ointment, cream or lotion. A spray form has also been proposed which would result in a more concentrated amount of the active ingredient on the skin due to evaporation. The sprayable liquid, in addition to varenicline, comprises a phospholipidic gel-forming agent, ethanol, phosphate buffer and distilled water [61]. A clinical trial assessing the absorption of varenicline into the body from a varenicline solution has been completed (NCT00774605 in 2009).

Relative efficacy

Results from the clinical trials have yet to be released; however, these novel formulations are likely to be as, if not more, efficacious than traditional formulations [41]. Slow release drug formulations often lead to better compliance and maintenance of plasma levels of the drug in therapeutic ranges [62]. The free-based patch form of varenicline will have the advantage of administrating a steady infusion of the drug over an extended period of time and adverse effects or therapeutic failure, which are often associated with intermittent dosing, will be avoided [63]. Free base varenicline solution have been shown to reduce nicotine administration in rats dose-dependently [64].

Relative safety

The reduced rate of passage and absorption of the controlled-release tablet formulation aims to reduce side effects associated with varenicline such as nausea [59]. Previous studies have shown that controlled-release bupropion reduces incidences of side-effects leading to treatment discontinuation [65]. There is also evidence to suggest that controlled-release medications are less likely to be abused or misused [62]. Free-base patches have an even better safety profile, in that drug input can be terminated at any point by removing the patch. However, they may lead to other side effects including skin irritation [63].

Relative cost

New galenic formulations are likely to be similar in price to traditional formulations of varenicline [66], which currently costs around £164 (US$ 240) for 12 weeks [67].

Relative use

The introduction of traditional formulations of varenicline in the US resulted in a net increase in use of stop-smoking medications [68, 69]. However, since speculation of an association between varenicline and cardiovascular disease and suicidal idealisation, prescription rates have fallen [70-72].

Unless such concerns are reduced, new galenic formulations may not have a dramatic impact on overall effective mediation use.

Relative scope

New galenic formulations may be suitable for those patients who have failed with other medications but experience side effects with the traditional formulations of varenicline.

Relative ease of use

Controlled-release varenicline is in oral drug form which has the notable advantage of easy administration and free-based patches may improve compliance by simplifying the medical routine [63].

3.2 Alternative Products: efficacy or likely efficacy

3.2.1 Cytisine

Cytisine (marketed as Tabex) is a plant-based alkaloid found in members of the *Leguminosae* family. Like varenicline, it acts as a partial agonist of nAChRs and has a half-life of around 4.8 hours [73]. However, it would be wrong to suggest that this is a novel product worldwide. In fact, cytisine was developed as a treatment for tobacco dependence in Bulgaria in the early 1960s, and is still commercially available in Central and Eastern Europe.

Relative efficacy

Cytisine's initial distribution was restricted by early studies showing that it had poor absorption rates and limited effects on the brain [74, 75]. However, the 2006 positive review by Etter et al [76] and licensing of varenicline, which has a similar mechanism of action, brought renewed attention. Since then a number of studies have demonstrated its efficacy. A pragmatic, open-label, non-inferiority trial with 1310 adult daily smokers, noted that when combined with behavioural support, cytisine promotes continuous abstinence at 6 months to a greater extent than NRT; while a Cochrane systematic review reported that cytisine was four times more effective than placebo [77, 78].

Relative safety

Cytisine appears to have a greater number of side-effects than NRT, including gastro-intestinal problems [79], headaches, irritability, nausea, constipation and tachycardia [76]. Cytisine is also contraindicated for people with arterial hypertension and advanced atherosclerosis [76].

Relative use

Cytisine is more cost-effective than currently licensed products, and so may be pivotal in helping to reduce social-inequalities in smoking cessation [80]. The cost of a course of cytisine is generally about 10 to 20% that of varenicline (US$12 for full treatment) [80]. However, its development is hindered by the substantial investment that would be required to meet licensing requirements, and as a result, its advantage of being low cost may be lost in the process [81].

Relative scope

Given evidence that decreasing the price of treatments increases overall use of medication for smoking cessation [82], its presence in the world-wide market may increase overall use of effective medications. Evidence suggests a higher prevalence of smoking cessation aid use in Eastern Europe where cytisine is licensed as a smoking cessation aid relative to Southern Europe [83].

Relative scope

Due to its low cost, cytisine is likely to be beneficial for patients in developing countries and to be beneficial for those contraindicated for other medications. Indeed, combined use of nicotinic partial agonists and NRT is well tolerated [84]. It is derived naturally from the seeds of the plant *Cytisus laborinum*, which may be an important characteristic for smokers who do not wish to use a synthesised drug.

Relative ease of use

The most common dosing is 2-6 1.5mg tablets per day, which is greater than the oral dosing for varenicline but lower than the recommended dosing for non-transdermal nicotine products. For those patients who do not like oral administration, cytisine is also available as a film which is placed between the gum and lip and dissolves over time [76].

3.2.2 Nortriptyline

There was a rapid expansion of research into other antidepressants for smoking cessation following the advent of bupropion, with nortriptyline becoming a popular second-line treatment in many countries [85]. Nortriptyline is a tricyclic antidepressant, named after its chemical structure which contains three rings of atoms.

Relative efficacy

Nortriptyline has similar efficacy to both bupropion and licensed NRT [86]. Six-placebo controlled trials have shown that nortriptyline doubles quit rates [87]. A recent pragmatic randomised controlled trial of 901 smokers reported that prolonged abstinence at six months was 34% more likely among those

receiving nortriptyline plus NRT relative to placebo plus NRT [88]. In this trial, nortriptyline was also found to reduced depression and anxiety but urges to smoke did not differ between groups.

Relative safety

Nortriptyline is believed to have similar effects on dopaminergic and adrenergic systems as bupropion, but tends to have greater side effects. These include dry mouth, urinary retention, constipation, sexual difficulties and seizure risk [87]. When used in combination with NRT excessive sweating and feeling shaky have been reported [88]. Concerns have been raised regarding the use of tricyclics for treatment of depression because of concerns about toxicity in overdose.

Relative cost

Nortriptyline is proposed to be much cheaper than bupropion. For example, in the Netherlands one month of treatment with bupropion costs around €71.48 (US$ 81) compared with €12.22 (US$ 14) for nortriptyline [89]. Nortriptyline also appears to have equivalent cost-effectiveness, supporting its utility [90].

Relative use

Nortriptyline has become a popular second-line treatment for smoking cessation in many countries, including New Zealand [91].

Relative scope

As with bupropion, Nortriptyline is likely to be particularly useful for those suffering from depression. However, it is contraindicated in those who have experienced myocardial infarction, have arrhythmias or severe liver disease. Thus, the medication is generally only used for those who fail with, have an adverse event in response to, or have a contraindication for, one of the first-line medications [19]. Many smokers may also be adverse to using a drug associated with treating psychiatric conditions.

Relative ease of use

Nortriptyline has a similar dosing profile to varenicline and bupropion: one oral tablet of 25 to 100mg per day or titrated dosages to serum levels recommended for depression.

3.2.3 Electronic cigarettes

Electronic cigarettes (e-cigarettes) are battery powered devices consisting of a cartomizer usually containing a mixture of nicotine, water, flavourings and propylene glycol or glycerine which produces a nicotine aerosol. Since e-cigarettes were first introduced into the market in 2003, there have been

significant developments to make them more efficient and appealing [92]. Regulation of e-cigarettes varies widely from country to country. Many countries have banned them (e.g. Brazil, Canada, Seychelles, Uruguay, Norway and Singapore), others have imposed heavy restrictions; and some have licensed them as medicines [93, 94] (e.g. in the UK: e-Voke produced by British American Tobacco [95]).

Relative efficacy

Only two RCTs have assessed e-cigarette use for smoking cessation, with a combined sample size of 662 participants. In both trials, early generation devices with low levels of nicotine were used. Pooled data from these two RCTs showed that use of nicotine-containing e-cigarettes was associated with higher abstinence rates relative to placebo, comparable abstinence rates to NRT, and a greater chance of reporting reductions in cigarette consumption of over 50% [96]. Although further trials are needed [96], similar efficacy has been noted in survey based studies [96-100].

Relative safety

There is no doubt that e-cigarettes are substantially less harmful than cigarettes since they do not contain tobacco, which when lit produces over 3,000-4,000 chemicals, many of which are carcinogenic [101]. Studies have identified a number of toxic chemicals in e-cigarette liquid (tobacco specific nitrosamines and diethylene glycol [102]; amino-tandalafil and rimonambant [103]; carbonyls (formaldehyde, acetaldehyde and acrolein) [104]; heavy metals (nickel, lead and cadmium) [104]; silicate particles [105]). However, the general consensus is that levels are low, unlikely to do harm, are substantially lower than those found in cigarettes; and in some cases, are similar to those found in NRT (e.g. nitrosamines) [106-108]. Nonetheless, continuous monitoring is warranted given the ever-changing product landscape.

Relative cost

A single disposable e-cigarette costs around £6 (US$ 9). Newer generation starter kits cost anything from £17 to £90 (US$ 25 to 130), with a refill costing between £2 (US$ 3) and £4 (US$ 6) [109], which is less than or as expensive as purchasing NRT [110]

Relative use

The presence of e-cigarettes in the UK market appears to have increased the number of smokers using non-tobacco nicotine containing products [56]. Thus, it is likely that e-cigarettes are enticing new smokers to use smoking cessation aids rather than monopolising the current medications market.

Relative scope

E-cigarettes are likely to be attractive for those smokers who miss the sensory and behavioural aspects of smoking. Currently available medicinal products, with the exception perhaps of some non-transdermal NRT, do not provide a similar sensation to smoking. E-cigarettes may be particularly suitable for those who have failed with other smoking cessation aids or for those whom these aids are contraindicated.

Relative ease of use

E-cigarettes provide the sensory and behavioural aspects commonly associated with smoking, i.e. the hand-to-mouth action. Smokers therefore often report they are more satisfying than NRT and so adherence is likely to be greater [111]. However, smokers must correctly change/fill cartridges and charging is required for the new generation products.

3.2.4 Clonidine

Given that anxiety is a symptom of nicotine withdrawal following smoking cessation [112], it has been proposed that the anxiolytics clonidine, a noradrenergic agonist, may be a possible smoking cessation treatment [113, 114]. Following evidence for its safety and efficacy, clonidine hydrochloride is now recommended as a second-line agent, but is not approved by the Food and Drugs Administration or any other drug regulatory body as a smoking cessation aid [115].

Relative efficacy

Studies have shown that clonidine relieves cravings, anxiety, restlessness and tension [113, 114]; and appears to promote smoking cessation, with beneficial effects particularly among those with high levels of anxiety [116]. A randomised clinical trial in 1988 with smokers who had failed in previous attempts to stop smoking reported that cessation success rates in clonidine treated subjects (verified by serum cotinine concentration) was more than twice that in placebo-treated participants [113]. The same year, another randomised placebo-controlled trial with forty cigarette smokers reported that clonidine treatment ameliorated short-term withdrawal symptoms, especially cravings, and that there was a trend towards a reduction in the number of cigarettes smoked [117]. However, another randomised trial with nearly two-hundred subjects failed to report a benefit on withdrawal symptoms, quitting or smoking reduction in a primary care setting [118].

Relative safety

Clonidine has adverse effects associated with its use: postural hypotension, dizziness, dry mouth, sedation, sleep disturbances, depression, and constipation [116]. Although these are also classic

withdrawal symptoms and may not result from drug use, this has resulted in the avoidance of clonidine by many clinicians [119].

Relative cost

Oral dosing of clonidine is relatively inexpensive (<$1 per day) compared to NRT or bupropion which cost more than $3.00 per day [120]. Thus if clonidine is deemed as effective as the first-line treatments it is likely to result in a reduction in health care costs.

Relative use

Although clonidine is not currently licensed as a smoking cessation aid, and its side-effects mean that is it unlikely to compete with the currently available first-line treatments, it is regarded as second-line treatment in a number of countries.

Relative scope

Clonidine may be particularly useful for those with anxiety problems and appeal to smokers who do not wish to use nicotine-based medications to make a quit attempt, or who have previously tried unsuccessfully to quit with other pharmacotherapy. However, many smokers are adverse to using a drug associated with treating psychiatric conditions [112]. Caution is also advised when co-administering clonidine with beta-blockers, calcium channel blockers and digitalis [116].

Relative ease of use

The regimen is similar to that for the prescription first-line treatments and clonidine is also available as a patch which may increase adherence rates [121]. Patch formulations of smoking cessation medications are discrete, provide a steadier supply of the drug, and can be simpler to use than oral formulations.

3.3 Alternative Products: unclear efficacy

3.3.1 Venlafaxine

Smoking is particularly high among those suffering from depression, thus anti-depressants may be a suitable pharmacotherapy for smoking cessation for such individuals [122]. Venlafaxine, an Serotonin-noradrenaline reuptake inhibitor (SNRIs), inhibits neural 5-HT, noradrenaline and dopamine reuptake, and is used in the treatment of depression and anxiety disorders [86].

Relative efficacy

Preliminary evidence also suggests that venlafaxine may have therapeutic effects when combined with NRT through its influence on improved memory and reduction in depressive symptoms [123]. In a study of nearly one hundred and fifty smokers randomly assigned to Venlafaxine plus NRT or placebo plus NRT in conjunction with behavioural counselling, venlafaxine did not appear to increase the propensity to quit smoking. However, this trial suggested that there may be benefits for lighter smokers and a reduction in negative affect was noted [124].

Relative safety

Side effects of SNRIs are greater than for SSRIs and bupropion and include muscle spasms/twitching, profuse sweating and dizziness [125, 126]. Controlled trials assessing the use of venlafaxine for the treatment of depression have noted excessive weight gain and sexual dysfunction [127]. Cardiac electrophysiological effects with venlafaxine have also been observed in guinea-pig cardiac myocytes [128]. However, venlafaxine does have a more benign side effect profile than older anti-depressants.

Relative cost

The cost for six months treatment of venlafaxine for depression is similar to bupropion at around £1530 (US$ 2213) [129], and therefore significantly more than for NRT. Its cost-effectiveness for smoking cessation and harm reduction has not been assessed.

Relative use

SNRIs greater number of side effects means that they are unlikely to be licensed as smoking cessation aids, unless efficacy is proved to be substantially greater than for first-line treatments.

Relative scope

Due to its anti-depressive properties, venlafaxine may be an appropriate medication for those with comorbid depression diagnoses. However, its inability to mimic the sensory and behavioural components of smokers, and greater side-effects compared to the medications discussed so far, may limit its use.

Relative ease of use

Dosages of 75 to 375mg/day administered as 2 or 3 times daily regimens produce significant reductions in depression [130]. If similar levels are used for smoking cessation the regimen is more complex than the single daily dose of either varenicline or bupropion but simpler than for oral NRT.

3.3.2 Nicotinic acetylcholine receptors (nAChR) antagonists

Given the proven efficacy of varenicline, a partial agonist of nAChr, it has been suggested that nAChR antagonists may aid smoking cessation [131]. Such drugs include mecamylamine (trade name Inversine), currently approved for the management of hypertension; lobeline, an alkaloid derived from the leaves of an Indian tobacco plant (*Lobelia inflate*) [75, 132]; GTS-21, a derivative of anabaseine (a product in tobacco), which improves cognitive function and may be a possible novel treatment for dementia [133]; dianicline, a drug developed by Sanofi-Aventis which has a similar pharmacological profile to varenicline; sazetidine specified for the treatment of anxiety and depression; UCI-30002, a negative allosteric modulator of nAChr and agonist of GABA receptors [134]; and AT-1001 [N-(2-bromophenyl)-9-methyl-9-azabicyclo[3.3.1] nonan-3-amine], a high-affinity and highly selective ligand at nARhr [135].

Relative efficacy

Mecamylamine has shown some promising results [136], particularly in women [137]. Lobeline has proved rather ineffective [75, 132]. The effects of GTS-21 on negative affect, cognition and smoking relapse are currently being investigated in a phase two clinical trial (NCT02432066). Some have argued that it may prove a better treatment option than the nicotine patch [138] and may be particularly beneficial for those with schizophrenia, as it appears to improve symptoms [139]. Clinical development of dianicline has been discontinued after reports of unfavourable results in phase 3 studies (Sanofi Pipeline, 2012). AT-1001 has been found to decrease nicotine self-administration in rats and to be a potent partial agonist with 65-70% efficacy at human nAChr [140]. UCI-30002 has also been shown to decrease nicotine self-administration [141].

Relative safety

Lobeline and mecamylamine have significant side effects [75, 132], including drowsiness, hypotension and constipation [142, 143]. GTS-21 is no more toxic than nicotine and does not appear to affect either autonomic or skeletal muscle systems. Clinical trials suggest that it is well tolerated in large doses [133]. Dianiclin may have a more favourable profile than varenicline [41], while sazetidine has fewer neurologic side effects than other nicotinic agonists [144].

Relative cost

The cost effectiveness of these products for smoking cessation has not been assessed.

Relative use

None of these products are licensed for smoking cessation and many are in the early stages of clinical trials, thus it is not possible to predict the likely impact they may have in the future.

Relative scope

Mecamylamine was original marketed for lowering blood pressure, and so may be particularly beneficial for those with certain cardiovascular conditions. It is easy to use and can be combined with NRT. In fact, the two therapies may offset each other's adverse effects [136, 143]. GTS-21 has been proposed as a possible treatment option for patients with schizophrenia [145].

Relative ease of use

Dosing is similar to bupropion and varenicline, with a recommended 8mg tablet once daily of lobeline and a 150 mg twice daily dose of GTS-21 (NCT02432066). However, many smokers are adverse to using oral medication and prefer transdermal product forms.

3.3.3 Glucose tablets

Oral dextrose (glucose) has been proposed as a possible aid to smoking cessation. It was hypothesised that glucose tablets could promote abstinence by satiating carbohydrate cravings that ex-smokers often mislabelled as cigarette cravings [146, 147]. Previous studies have shown that nicotine acts as an acute appetite suppressant by raising blood glucose levels and acting directly on cells in the lateral hypothalamus. The appetite suppressant effect may also be linked to the effects of nicotine on serotonergic pathways in the brain [146].

Relative efficacy

In a randomised controlled trial with nearly one thousand participants, no significant effect of glucose tablets over and above sweet tasting tablets was detected [147]. However, glucose tablets may promote short-term abstinence, particularly when used as an adjunct to NRT or bupropion [147, 148].

Relative safety

Part of their appeal lies in their reduced number of side effects relative to the first-line treatments [146]. When used in small doses, no common side effects have been reported; however, at higher doses allergic reactions have been noted and its use among diabetic patients should be avoided.

Relative cost

The major advantage of glucose tablets is that they are relatively inexpensive and thus they may be a treatment option for developing countries [146].

Relative use

Given their lower cost and accessibility the promotion of glucose tablets for smoking cessation would likely increase the overall use of smoking cessation medication particularly in developing countries.

Relative scope

Glucose is unlikely to interact with other medications and so may be used concurrently [147]. It is freely available and has no contraindications (except some caution should be advised for those with diabetes). This is important given that many smokers are being treated for smoking related morbidities with pharmacotherapy.

Relative ease of use

Glucose tablets are freely available in shopping outlets, unlike burpoprion and varenicline which are only available on prescription. Recommended daily use is similar to that for NRT [147].

3.3.4 Nicotine vaccines

Vaccines targeting nicotine are being developed as a novel approach to treating tobacco dependence. The main mechanism of action is their inducement of anti-nicotine antibodies that bind to nicotine in the periphery, and thus reduce the amount which enters the brain. Vaccines may also have a secondary effect of slowing the rate of nicotine delivery; an important property, as rapid increases in nicotine levels are more likely to lead to addiction than slow kinetics [149]. First-generation formulations were conjugate vaccines, consisting of nicotine linked to a carrier protein and then mixed with alum adjuvant [150]. Modifications and further developments have focused on finding the most effective site of attachment for nicotine, identifying the number of nicotine molecules which need to be linked to each carrier protein, and the composition of the protein itself [150, 151]. To increase efficacy, support has been given to the use of multivalent vaccines, i.e. combination of multiple vaccine products and concurrent use with other smoking cessation pharmacotherapy [152]. Animal studies have shown a strong synergistic effect of a nicotine vaccine in combination with the nAChR antagonist mecamylamine [153].

Recently, the first synthetically engineered nanoparticle nicotine vaccine - SEL-068 - designed by Selecta Biosciences Inc, entered a phase 1 clinical trial to evaluate its safety, tolerability and pharmacodynamics profile [154]. As it is fully synthetic, the immune response will focus on nicotine, thus avoiding responses to biological carriers. Alternatives to nicotine vaccines have also been suggested. These include passive immunization, which unlike vaccines does not require weeks to months for the generation of effective levels of antibodies; and gene transfer, which involves the administration of viral vectors containing genes for the expression of drug-specific antibodies [155].

Relative efficacy

First generation nicotine vaccines were shown to clinically reduce the amount of nicotine reaching the brain and to reduce nicotine self-administration behaviours [156-161]. However, these strong preclinical findings were not subsequently mirrored in clinical trials, with overall efficacy for smoking cessation being similar to placebo vaccines [162-164]. This may be a consequence of poor antibody production or vaccine composition. Many vaccines produce nicotine-specific antibody levels not much above 50-100 μg/ml, which provides the binding capacity for at most one cigarette [150]. Subgroup analyses have shown that subjects with the highest serum antibody concentrations have double the smoking cessation rates of controls [163, 165]. It also appears that nicotine vaccine candidates which incorporate hapten enantiopurity may maximize efficacy compared to use of racemic nicotine hapten [166]. However, a recent study concluded that nicotine vaccines do not appear to improve the chances of stopping smoking when given in addition to varenicline and behavioural support [167].

Passive immunization with drug-specific monoclonal antibodies has been shown to block nicotine [153], while preclinical tests on monkeys immunized with increased doses of the synthetically engineered nanoparticle nicotine vaccine SEL-068 showed a robust and dose-dependent induction of high titres of anti-nicotine antibodies with a strong affinity to nicotine [168]. In a recent study, SEL-068 was shown to attenuate nicotine's discriminative-stimulus effects in nicotine-experienced monkeys [169].

Relative safety

The safety profile of vaccines has been confirmed in clinical trials and is likely to be similar to that of other medications, although further surveillance is warranted [170]. In view of the novelty of gene transfers and possible unanticipated toxicities, evidence for long-term safety will be necessary for their development to proceed.

Relative cost

Although a nicotine vaccination program was not found to be cost-effective for smoking prevention [171], there is some suggestion that vaccines will be less expensive than other smoking cessation treatments [172]. Costs are likely to be higher for passive immunization vaccines, with dosages required which are 10-100 times greater than those widely used to treat cancer or immune disorders [173].

Relative use

The effect of overall effective medication use is unclear. However, given that the majority of smokers obtain medication over-the-counter [174], the requirement that it be administered by a health-care professional means that few smokers are likely to opt to use nicotine vaccines.

Relative scope

Nicotine vaccines may be suitable for those with contraindications for other smoking cessation medication. Long-term the treatment regimen for vaccines is simple and they may be preferable for those with poor adherence.

Relative ease of use

Although multiple injections of the first generation vaccines are required intravenously by a health care professional, they have a prolonged effect on the immune system (for 6-12 months). Passive immunization vaccines in contrast do not require weeks to months for the generation of effective levels of antibodies.

3.3.5 Drugs that affect gamma-aminobutyric acid (GABA) transmission

Nicotine stimulates the release of a number of neurotransmitters, including GABA. Thus it has been proposed that medications that affect GABA neurotransmission may be useful as pharmacological treatments for tobacco addiction [175, 176]. One example is topiramate which inhibits glutamatergic neurotransmission, reduces fast inward voltage-gated sodium currents [177], and enhances GABAergic tone by direct action on GABA-A receptors [178, 179]. Topiramate is approved for the treatment of epilepsy and has been shown to be efficacious for bipolar disorder, post-traumatic stress disorder and eating disorders (e.g. [180]). Low dose topiramate has also been used in the treatment of alcohol dependence [181]. Three other drugs which may also offer some utility for smoking cessation include zonisamide which is in the same class of medications (marketed as Topamax) [182]; gabapentin, an antiepileptic drug that acts on voltage gated calcium channels (particularly N and L-types) and binds to GABA-B receptors to inhibit their function[183, 184]; and tiagabine, a blocker of GABA reuptake (marketed under Gabitril) [185, 186].

Baclofen, a selective GABA-B receptor agonist, was recently proposed in response to the observation of a co-occurrence between alcohol and nicotine use. Approximately half of the population who are dependent on alcohol smoke, 75% of whom require treatment for both dependences [187, 188]. Up until this point, drugs to tackle both addictions had proved unsuccessful.

Relative efficacy

Studies have demonstrated the efficacy of topiramate for smoking cessation, particularly among men and alcoholic smokers [189-191]. An additional benefit may be the prevention of post-cessation weight gain [192]. In a recent 10-week trial, topiramate resulted in higher quit rates than a placebo and significant decreases in weight [193]. Zonisamide also appears promising. Its combination with

varenicline increases smoking quit rates and decreases nicotine withdrawal and craving relative to varenicline alone [182]. Studies on tiagabine suggest that it may reduce the rewarding effects of nicotine and improve cognitive performance in abstinent smokers [185].

A number of studies have provided clinical and preclinical evidence that baclofen is a successful treatment for both tobacco addiction and alcoholism [175, 194]. A recent randomized placebo-controlled pilot trial demonstrated a significant reduction in craving and smoking [195]; while another that baclofen significantly increased the percentage of days of abstinence from alcohol and tobacco co-use [196]. A further trial was terminated due to difficulties in recruiting an appropriate sample (NCT01228994).

In pre-clinical trials gabapentin was shown to attenuate withdrawal symptoms and increase short-term abstinence [197]. However, two small scale trials showed little promise of gabapentin for treating smoking cessation [198, 199]. This was confirmed in a recent proof-of-concept pilot study [200].

Safety

In general, the safety and tolerability of GABA-based drugs have been confirmed [195]. However, they may be liable to abuse [201] and have side effects including sedation, dizziness, weakness, and fatigue [195]. In a trial of twelve smokers treated with topiramate additional side-effects including slurred speech, depressive symptoms and fatigue were noted and three subjects interrupted treatment due to intolerable symptoms [202]. Zonisamide is slightly better tolerated than topiramate and does not produce the negative cognitive effects that are evident following topiramate administration [203, 204]. However, those using antiepileptic drugs, such as tiagabine, may be at risk of developing severe neuropsychiatric symptoms [205].

Relative cost

Topiramate and Gabapentin costs less than £4 (US $6) a week compared with at least £9 (US $14) for NRT [206, 207].

Relative use

It is currently unclear whether GABA-based drugs would increase the overall use of effective medication. Although cheaper than nicotine-containing products they would likely not be available over-the-counter.

Relative scope

GABA-based drugs may be useful for smokers who wish to prevent post-cessation weight gain and may act as a concurrent treatment for epilepsy, migraines, some psychiatric conditions and eating

disorders (conditions for which they were originally indicated). Baclofen may be suitable for those with co-existing alcohol use disorders.

Relative ease of use

Many GABA-based drugs, including baclofen, must be taken every 4-6 hours and preferably with clinical supervision to ensure compliance [194-196]. Thus they do not appear to be easier to use than currently available drugs which are administered orally. Although extended-release formulations have been produced for multiple sclerosis patients, these have not received approval for smoking cessation (NCT01457352).

3.3.6 Drugs that affect N-methyl-D-aspartate (NMDA) receptors directly or indirectly

The finding that one of the effects of nicotine on the body is at the level of NMDA receptors in the brain motivated investigations into drugs which affect these receptors. Four drugs have been, or are currently being, assessed in clinical trials which appear to directly affect NMDA receptors: memantine, a non-competitive, selective NMDA receptor antagonist used in the clinical treatment of dementia (NCT00136786 still running), GW468816, a competitive antagonist at the glycine site [208], and the NMDA receptor partial agonist cycloserine (NCT01062932 in 2012). Gabapentin (discussed already) also directly inhibits NMDA receptors and potentiates the effect of NMDA channel blockers [209-211].

A further drug, *N*-acetylcysteine [212], has an indirect effect through the release of glutamate from glia into the extra-synaptic space via the cysteine-glutamate antiporter [213]. This increased basal glutamate activates type II/III metabotropic glutamate receptors (also extra-synaptic), which supresses the release of synaptic glutamate [214], thereby reducing NMDA receptor activation. Furthermore, N-acetylcysteine is a precursor for gamma-glutamylcysteinslycine, which has been shown to potentiate NMDA receptor responses [215, 216]. N-acetylcysteine also stimulates the release of dopamine [217], which is argued to play a major role in drug addiction [218].

Relative efficacy

Memantine has demonstrated some efficacy for other dependencies including opioid use [219]. However, in a small study of 20 smokers, memantine failed to facilitate smoking reduction [220]. Despite preclinical data being promising for GW468816, no effect on relapse or lapse rates have been reported relative to placebo [208]. Initial studies on cycloserine provided some support for its use with cue exposure therapy in attenuating conditioned reactivity to smoking cues [221], but further development hinges on the results from the clinical trial. Finally, a pilot study exploring the effect of *N*-acetylcysteine has shown encouraging trends [212]. A recent review on the potential role of *N*-acetylcysteine in the management of substance use disorders concluded that it shows promise in

terms of safety, tolerability, and potential efficacy for promoting abstinence from cocaine, nicotine, and cannabis [222].

Relative safety

Although higher-affinity NMDA-related drugs can produce severe adverse neurotoxic and psychogenic effects in humans, and lower affinity drugs are likely to have a greater number of side-effects than NRT, data across a range of clinical applications has shown that NMDA-based drugs are safe and well-tolerated [223].

Relative cost

NMDA-related drugs are a similar price to NRT. For example, twenty-eight tablets of 10mg memantine costs around £34.50 (US$ 39) [224].

Relative use

It is currently unclear whether NMDA-related drugs would increase the overall use of effective medication. If only available on prescription, use is unlikely to cannibalise the NRT market.

Relative scope

NMDA-related drugs were initially indicated for Alzheimer's disease, having a significant positive effect on cognition and behaviour. NMDA based drugs also have anti-anxiolytic and anti-depressant effects, so may be a suitable treatment for smokers suffering from mood disorders [225].

Relative ease of use

Drugs targeting NMDA receptors are administered orally, but generally require only one tablet per day. Dosing routines are therefore simpler than for oral NRT but similar to varenicline and bupropion. However, many smokers are adverse to using oral medication and prefer transdermal product forms.

3.3.7 Dopamine agonists

As mesocorticolimbic dopamine systems mediate the reinforcement effects of nicotine [226], researchers have hypothesised that drugs traditionally used to treat Parkinson's disease and appetite control disorders which affect dopamine receptors may be potential targets. Viable candidates for clinical investigation are levodopa [227], bromocriptine, GSK598809, the cognate analog GSK618334 and BP1.4979 developed by the Bioproject.

Relative efficacy

Preliminary evidence in rats suggests levodopa may aid in preventing post cessation weight gain by diminishing dopaminergic responses to external stimulation [228]. Levodopa does not appear to promote abstinence or withdrawal symptom relief [227]. Bromocriptine has been shown to decrease cigarette craving and reduces smoking rates in humans [229, 230].

Animal studies have shown that GSK598809 decreases nicotine seeking behaviour and nicotine cravings [231]. Phase 1 and phase 2 trials have since been conducted with human participants, but with mixed results. One clinical trial found that a 75mg dose alleviated craving in smokers after 14 hours of overnight abstinence. It also partially reversed attentional bias, though such effects were not maintained at later time points (NCT00437840 in 2008). In another trial, which included a placebo control group, a single dose of GSK598809 did not reduce the reinforcing value of smoking and nicotine when measured using the Behavioural Economic Task and Cigarette Choice Paradigm. In fact, when smokers were allowed to smoke freely, those who had received the active drug had higher cigarette consumption, suggesting some compensatory behaviour (NCT00605241 in 2012). GSK598809 was also recently tested in a third trial as an add-on to cognitive behavioural therapy and nicotine patch replacement therapy for the prevention of very early relapse from smoking in severe chronic smokers (NCT01188967 in 2014). Due to the potential cardiovascular liability at high doses, each patient in the trial was required to use an ambulatory monitor, which was a significant hurdle to recruitment. The results of this trial have yet to be reported.

GSK618334 entered clinical trials around the same time, in 2007 (NCT00513279 in 2010, NCT00814957 in 2009, NCT01036061 in 2011). These focused on its safety profile and pharmacokinetics, showing promising results. However, the drug has yet to be tested as a smoking cessation aid. A phase 2 clinical trial assessing the efficacy and safety of BP1.4979 for smoking cessation was completed at the beginning of 2015 (NCT01785147 in 2015), but results have yet to be published.

Relative safety

Many new drugs which target dopamine receptors have possible cardiovascular liability at high doses. Suitable data on the safety profile of drugs which target dopamine receptors is currently unavailable. Side effects of bromocriptine and levodopa have hindered their recommendation for smoking cessation [232].

Relative cost

Potential costs of these new drugs which target dopamine receptors are unclear. Previous studies have reported that dopamine agonists cost significantly more than other medications which have been tested as smoking cessation aids [233].

Relative use

It is unclear whether these novel drugs which target dopamine receptors will increase the overall use of smoking cessation aids. Currently evidence regarding efficacy is mixed, which, in addition to their likely high cost, may hinder use.

Relative scope

New drugs targeting dopamine receptors may be effective for the concurrent treatment of alcohol dependence and for those who wish to prevent post-cessation weight gain [234].

Relative ease of use

New drugs targeting dopamine receptors are available in dosages of 60mg to 175mg tablets. Thus, the regimen will likely consist of one tablet per day which is less than that for oral NRT. However, many smokers may not wish to use oral medication and prefer transdermal product forms.

3.3.8 Noradrenaline reuptake inhibitors

Preclinical and clinical studies suggest that noradrenaline contributes to the mediation of the subjective effects of tobacco [235]. The noradrenaline reuptake inhibitor atomoxetine (marketed as Strattera), used in the treatment of attention deficit disorder, may thus be a useful aid for smoking cessation [236]. Atomoxetine causes noradrenergic augmentation in the prefrontal cortex [237]. The alpha- and beta-adrenergic receptor blockers carvedilol (marketed as Coreg and Dilatrend) and labetalol have also been suggested as harm reduction treatment options for tobacco dependence given that they may dampen the cardiovascular response to nicotine [238]. Reboxetine, a selective noradrenaline uptake inhibitor prescribed as an antidepressant, was also advocated as a possible treatment option [239]. Although reboxetine received preliminary approval by the FDA in 1999 as an antidepressant, due to its positive pharmacological profile and lack of side effects, its development has been halted [240].

Relative efficacy

Trials using clinical populations (psychiatric patients, non-psychiatric patients and patients with attention deficit hyperactivity disorder) show tentative support for the possibility that atomoxetine may reduce cigarette consumption and/or smoking behaviours [236, 241, 242]. In healthy populations, atomoxetine has been found to reduce the number of cigarettes smoked, but does not result in lower salivary cotinine levels relative to placebo [243]. A recent RCT which aimed to assess atomoxetine's effects on nicotine response and stress response in smokers was suspended due to a lack of funding (NCT02046551).

Carvedilol and labetalol treatment has been found to attenuate nicotine-induced increases in heart rate and blood pressure [244, 245]. Attenuation of tobacco withdrawal symptoms has been noted for high-dose labetalol treatment relative to placebo [245]. In contrast, the use of carvedilol alone or in combination with nicotine lozenges does not appear to affect withdrawal symptoms [244]. Carvedilol may also aid in the treatment of the physiological effects of smoking cessation, such as tremor and cough, by preventing or suppressing mucus hypersecretion [246].

Reboxetine has been found to attenuate nicotine self-administration in rats by over 60% [247], and to have an adaptive modification of the function of the selective noradrenaline transporters [248]. A patent has been approved to assess the use of an effective amount of reboxetine in combination with the administration of a smoking-cessation enhancing agent (e.g. NRT and an opioid antagonist) [249].

Relative safety

As atomoxetine does not raise concentrations of dopamine in the prefrontal cortex, it has low abuse potential, a finding that has been supported in clinical trials [237]. However, it is not well tolerated by healthy adults at high doses [243]. There are several clinical situations in which atomoxetine should be closely monitored or not taken including for patients who have a history of narrow angle glaucoma, cardiovascular problems, epileptic seizures, Tourette's syndrome, urinary obstruction, or who are pregnant [250]. Carvedilol is also contraindicated for a long list of conditions including, but not limited to, bradycardia, sick sinus syndrome, hepatic dysfunction, obstructive airways disease, severe hypotension, metabolic acidosis and phaeochromocytoma [251]. The safety and efficacy of once-daily carvedilol (25 or 50 mg) appears to be comparable to that of twice-daily labetalol (200 or 400 mg) [252]. Reboxetine is well tolerated by adults and the elderly during short- and long-term treatment for depression [253].

Relative cost

On the assumption that a one 40mg tablet of atomoxetine would be taken for 21 days [243], the cost would be in excess of £45 (US$ 65) per smoker for a three week period [254]; which is similar to the cost of many of the first-line treatments. Carvedilol and labetalol are much cheaper at around £0.06 per day (US$ 0.09) [255].

Relative use

It is unclear whether any of these drugs will increase the overall use of smoking cessation aids. However, given the current lack of evidence for their efficacy, they are unlikely to monopolise the smoking cessation market.

Relative scope

Given their original indication, atomoxetine may be beneficial for those suffering concurrently with attention deficit disorder and carvedilol for those with mild to severe congestive heart failure, left ventricular dysfunction and following a heart attack. However, there are several contraindications which need to be considered.

Relative ease of use

One tablet once or twice a day reflects the dosing profile of the first line treatments varenicline and bupropion. However, many smokers are adverse to using oral medication and prefer transdermal product forms.

3.3.9 PPARγ agonists

Down-regulation of pulmonary epithelial peroxisome proliferator-activated receptor gamma (PPARγ) by cigarette smoke promotes inflammatory pathways and contributes to chronic obstructive pulmonary disease (COPD) pathogenesis. Thus, it has been proposed that PPARγ agonists, such as pioglitazone (Actos) and OMS405 (originally OMS403), may be a suitable pharmacotherapy for harm reduction [256].

Relative efficacy

A preclinical trial of OMS405 for smoking withdrawal was conducted in the US in 2009 and a phase 2 clinical trial in 2010 [257]. Although the results have yet to be released, the patent literature reports a decrease in smoking behaviour in a manner similar to varenicline [258]. There is also evidence for a possible harm reduction indication for the drug. PPARγ agonists reverse the down-regulation of PPARγ through a number of pathways and help to improve symptoms of COPD, a disease which is largely due to smoking [259]. PPARγ agonists are currently also being assessed for their possible chemo-protective effects in relation to lung cancer [260].

Relative safety

OMS405 appears to have a good safety profile and can be used concurrently for the treatment of diabetes [261]. Water retention is a common side effect with other PPARγ based drugs and licensing cautions the use with patients diagnosed with cardiac disorders. Its safety relative to other smoking cessation aids is currently unclear [262].

Relative cost

A daily dose of 30mg OMS405 costs around £9 (US$ 13) a week, which is similar to the cost of NRT but cheaper than varenicline [263].

Relative use

It is unclear whether OMS405 will increase the overall use of smoking cessation aids. If it is less expensive and provides protective effects against inflammation it may have potential as a harm reduction product.

Relative scope

OMS405 was initially indicated for metabolic diseases, and thus may be a suitable treatment option for smokers diagnosed with diabetes.

Relative ease of use

OMS405 involves a daily 30mg dose, which is an easier routine than oral NRT products. However, many smokers may be adverse to using oral forms and prefer transdermal product.

3.3.10 Lorcaserin

Lorcaserin hydrochloride (marketed as BELVIQ and Lorqess) was approved in June 2012 by the Food and Drug Administration as an adjunct to a reduced-calorie diet and physical activity for chronic weight management. It is believed that lorcaserin decreases food consumption and promotes satiety by selectively activating 5-HT receptors in the brain [264]. It may thus be a suitable pharmacotherapy for smokers wishing to prevent post-cessation weight gain. A patent has recently been submitted to create a nutritional supplement for smoking cessation in which it is proposed that lorcaserin may be a main ingredient with the aim of increasing 5-HT levels and assisting in maintaining body weight [265]. In addition, lorcaserin used alone or combination with varenlicine may be a novel agent for smoking cessation given that 5-HT systems play key roles in the action of nicotine [266].

Relative efficacy

In preclinical studies, lorcaserin was found to decrease nicotine self-administration and nicotine-enhanced responding for conditioned reinforcement in rats [266-268]. A recent phase 2 clinical trial found that lorcaserin was associated with a significantly higher continuous quit rate compared with placebo. In addition, a reduction in bodyweight was also observed [269, 270]. A further phase 2 clinical trial is currently being conducted to assess the effect on urges to smoke, withdrawal symptoms, reinforcing effects of smoking and eating behaviour, in addition to body weight and abstinence (NCT02044874 still running).

Relative safety

Treatment with lorcaserin is well tolerated, with the most common adverse reactions observed being headache, dizziness, fatigue, nausea, dry mouth and constipation [269, 270]. However, neuropsychiatric and cognitive-related adverse events are frequent, and although no imbalance in reported cancer incidence in smokers is seen, mammary tumours have been found in rats treated with lorcaserin [271].

Relative cost

Lorcaserin has not been deemed a cost-effective weight loss strategy and costs substantially more (US$ 1,743 for full treatment) than traditional smoking cessation aids [272].

Relative use

The overall effect on effective medication use is unclear, but the high costs will likely limit its distribution.

Relative ease of use

Tested dosage in the clinical trial was 10mg lorcaserin once or twice daily which is similar to the dosing regimen of other smoking cessation medications [269]. It is currently only available in oral form which may not be suitable for all smokers.

3.4 Alternative Products: no efficacy

3.4.1 Other anxiolytics

Given the evidence for clonidine other anxiolytics have been proposed as possible aids to smoking cessation including buspirone (trade name Buspar), a non-benzodiazephine anxiolytic with effects on 5-HT neurotransmission; ondansetron (trade name Zofran), a5-HT3 receptor antagonist; and diazepam (first marketed as Valium) and meprobamate (marketed as Miltown and Equanil among others), which are tranquillisers. Beta-blockers also have potential anxiolytic effects and have been advocated. The idea behind the use of anxiolytics is that they moderate anxiety experienced from withdrawal symptoms and increase the main neural transmitters that play a major role in nicotine dependence [112].

Relative efficacy

As a whole, the findings from clinical trials suggest these medications have little effect on smoking cessation [86, 112]. For example, the rate of smoking abstinence has been reported to range from 36%to 88% and 16% to 89% in buspirone and placebo treatment groups, respectively. However, these

medications may have some effects on urges to smoke [273]. In a double-blind, randomised, placebo controlled trial, with forty long-term cigarette smokers, Buspirone ameliorated short-term withdrawal symptoms associated with smoking cessation [274]; while animal studies have demonstrated that ondansetron is effective in decreasing cravings [275]. Research into their utility has in recent years diminished due to the claim that the role of anxiety in smoking may have been overplayed [112].

Relative safety

Although many of these medications have significant side effects, such as risk of abuse and sedation [5], some have more favourable profiles: buspirone was advocated as it lacks abuse liability and does not promote dependence [276]. In a double blind, placebo controlled trial with around one hundred smokers, 4 week treatment with ondansetron was not associated with any severe side-effects [277]. In nine-hundred and eighty-four patients with generalised anxiety disorder who received buspirone in double-blind studies, the incidence of drowsiness did not differ significantly to that reported in placebo participants. Side-effects which did occur significantly more frequently include dizziness, headache, nervousness, light-headedness, paraesthesia and excitation [278].

Relative cost

It is likely that these products will be a similar price to clonidine and therefore cheaper than NRT [120]. A recent cost-effectiveness analysis of treatments for anxiety disorders found that benzodiazephines (like buspirone) were more cost-effective than tricyclic antidepressant drugs [279].

Relative use

Given their lack of efficacy and side effects, there is little justification for licensing them as smoking cessation aids.

Relative scope

These products may be particularly useful for those with anxiety problems and appeal to smokers who do not wish to use nicotine-based medications to make a quit attempt, or who have previously tried unsuccessfully to quit with other pharmacotherapy.

Relative ease of use

The regimen is likely to be similar as that for other first-line prescription medication, such as bupropion. Unlike NRT, they are only available in oral form and so may not be suitable for all smokers.

3.4.2 Selective serotonin reuptake inhibitors (SSRIs)

The SSRIs fluoxetine, paroxetine, sertraline, citalopram, and zimeledine (first-line treatments for depression) have been proposed as possible smoking cessation aids given that dysphoria, depressed mood, and a history of major depressive disorder, are related to uptake of smoking and a failure with attempts to quit [122]. The neurotransmitter 5-HT also plays a major role in nicotine's addictive effects [280].

Relative efficacy

Long-term trials of SSRI's and some short-term trials have failed to show efficacy in relation to smoking cessation among those with and without a diagnosis of depression [86, 281, 282], although there is some evidence to support the efficacy of sequential treatment (16 week treatment starting 8 weeks prequit) relative to standard treatment (10 week treatment starting 2 weeks prequit) [283]. A randomised placebo controlled trial found no evidence that fluoxetine treatment when used as an adjunct to NRT is effective, but that there may be an advantage to using it in depressed patients [284]. In another study, sertraline treatment produced lower self-reported withdrawal symptoms less irritability, anxiety and restlessness relative to placebo. However, abstinence rates did not differ [285].

Relative safety

Some side effects have been reported for the use of SSRIs for smoking cessation, particularly at high doses, including amblyopia (dimness of sight), gastrointestinal disorders, nausea, palpitations and tremors [284, 286]. Treatment with SSRIs has also been associated with emotional detachment, although controversy still exists on this issue [287]. SSRIs may have slightly more side effects than bupropion, including sexual dysfunction and weight gain [287].

Relative cost

There are currently no reports on the cost-effectiveness of SSRIs for smoking cessation; however, they do appear to be more cost-effective than the tricyclic antidepressants mentioned above when used to treat depression [288-290].

Relative use

SSRIs lack of efficacy for smoking cessation relative to the first-line treatment bupropion means that they are unlikely to be licensed for use as an aid to smoking cessation.

Relative scope

Given that SSRIs are first-line treatments for depression, they may be particularly suitable for smokers with a co-morbid diagnosis. However, evidence for their lack of efficacy means that they are unlikely

to be indicated for such purposes. Many smokers may also be adverse to using a drug associated with treating psychiatric conditions.

Relative ease of use

The dosing regimen of SSRIs is similar to that for other anti-depressants, including bupropion. However, unlike NRT, they are only available on prescription and do not address the sensory and behavioural components of smoking.

3.4.3 Silver acetate

Silver acetate use for smoking cessation is analogous to disulfiram for alcoholism being based on the principles of aversive conditioning. It works by producing an unpleasant metallic taste in the mouth when used in combination with smoking [291].

Relative efficacy

Although a possible effect in promoting cessation has not been disproved, any such effect is likely to be small, and less than that for NRT [291]. In a randomised trial of over five hundred participants, abstinence rates was higher in the silver acetate group compared to those receiving nicotine gum or ordinary gum but only among those with a lower weighted packyear consumption [292].

Relative safety

Excessive ingestion causes a rare condition called argyrism. Thus, a dose no greater than 756mg is recommended [291]. In randomised controlled trials side effects appear to be similar to that of nicotine replacement and are generally mild and transient, with the most common one being mouth irritation [292].

Relative cost

Its lack of efficacy means it is unlikely to be a cost-effective product for smoking cessation.

Relative use

Failure to show a beneficial impact on smoking cessation, its mechanism of action, and concerns over safety, means that silver acetate is highly unlikely to be licensed as a smoking cessation aid.

Relative scope

A particularly appealing aspect of silver acetate for smokers is its availability in both lozenge, gum and spray forms. However, its main mode of action, aversive taste, may be unappealing to some. There are also limits on the length of time it can be used, with the need to avoid argyrism [291].

Relative ease of use

Use is similar as for NRT: 2.5mg lozenge, 1.6mg gum, or 756mg spray used up to six times per day for three to six weeks. This is considerably more than for buproprion and varenicline and may thus adversely affect adherence rates.

3.4.4 Nicobrevin

Nicobrevin contains four 'active' ingredients (quinine, menthyl valerate, camphor and eucalyptus), and was claimed to provide sensory relief following smoking cessation [293]. There does not appear to be a clear mechanism of action for the use of menthyl valerate as a component of an anti-smoking preparation [294]. There is some evidence that cigarette smoking may have an effect on quinine pharmacokinetics [295], while oral camphor has been claimed to have carminative properties and eucalyptus is often used as a decongestant [294].

Relative efficacy

There is no evidence long-term that use of Nicobrevin can aid smoking cessation and insufficient evidence to support the efficacy of any of four ingredients it contains [293, 294]. Although it may be the case that it has effects on the respiratory and digestive systems, which may relieve some of the symptoms that smokers experience when quitting, any such benefits are eroded from the slightly higher relapse rates in actively treated groups [291, 294]. There have been no clinical trials comparing the use of Nicobrevin to the first-line treatments.

Relative safety

Concerns have been raised over the health implications of excessive quinine consumption in cigarette smokers [294]. Toxicity with camphor has been reported, while eucalyptus consumption is associated with nausea and vomiting [294]. Side effects associated with Nicobrevin include visual problems, skin irritation, and convulsions [294].

Relative cost

Nicobrevin is no longer available as a smoking cessation aid in a number of countries, and there is no evidence on its cost-effectiveness.

Relative use

Around 1 million packs of Nicobrevin were sold between 1992 and 1997. This number dropped to 6,600 packs between 2003 and 2008, while just 200 packs were sold in the subsequent two years

[294]. Following concerns over its safety, it has since been withdrawn in a number of countries, including the UK [294].

Relative scope

It lack of efficacy and withdrawal from the market in a number of countries means it is unlikely to be a suitable aid for smoking cessation.

Relative ease of use

Its oral formulation and dosing regimen means it is easier to use than some NRT products, however, some smokers may be adverse to taking medication orally. A 28 day course of 10mg tablets is generally recommended, starting with 1 pill in the morning and two at night.

3.4.5 Modafinil

Modafinil is marketed as a wakefulness-promoting agent for those who experience excessive sleepiness, including narcolepsy [296]. Its mechanism is elusive but involves the stimulation of histamine, noradrenaline, 5-HT, dopamine, and orexin systems in the brain [297].

Relative efficacy

Modafinil has demonstrated significant efficacy in cocaine dependence [150], and studies have shown its potential for alleviating tobacco withdrawal symptoms [298]. Subsequently, it was assessed for the treatment of smoking cessation [299], but the trial was terminated due to the detrimental effect of the drug. In the trial, quit rates did not differ among those who received modafinil relative to placebo, while smoking consumption was 44% higher in non-abstainers in the intervention arm. In another study, modafinil alone or in combination with nicotine lozenges did not affect tobacco withdrawal symptoms [300], although preliminary results from another study suggest that combining modafinil with transdermal NRT could provide complimentary effects [301].

Relative safety

Modafinil increases heart rate and systolic blood pressure so is likely to be contraindicated for those with cardiovascular disease. In one cross-over randomised trial, with nineteen participants increases in negative affect and withdrawal symptoms were noted [302]. An increase in baseline heart rate and systolic blood pressure was also noted.

Relative cost

A course of modafinil is around £120 (US$ 176) compared with around £164 (US$ 240) for varenicline. It is thus substantially more expensive than a course of NRT and so is unlikely to be deemed cost-effective given its lack of efficacy [303].

Relative use

As modafinil has significant side effects and lower efficacy than traditional smoking cessation aids it is unlikely to be licensed as an aid to smoking cessation or harm reduction.

Relative scope

Modafinil may be suitable for smokers who also suffer from sleep disorders (its original indication), but may be contraindicated for those with cardiovascular disease.

Relative ease of use

Dosing usually requires a daily load of 200mg. Thus the dosing regimen in easier than oral NRT but similar to bupropion and varenicline. Some smokers may however be adverse to taking medication orally.

3.4.6 Monoamine oxidase inhibitors (MAOI)

One factor which may account for the association between depression and smoking is monoamine oxidase (MAO), an enzyme first discovered over 40 years ago. Tobacco smoke contains MAOIs which act synergistically with nicotine to enhance addition potential. This is evidenced by smokers having lower levels of MAO compared with non-smokers [304]. Thus, it has been proposed that MAOIs, such as moclobemide, selegiline, lazabemide, and EVT302, may have synergistic beneficial effects on depression and smoking cessation.

Relative efficacy

Trials of moclobemide and selegiline when combined have failed to show efficacy for smoking cessation [86]. However, genetic markers in cholinergic loci in the 15q24 chromosomal region have been proposed to affect response and thus it may be possible to identify those likely to benefit from treatment [305].

Relative safety

MAOIs are contraindicated for bupropion use [306]. Selegiline is well tolerated by smokers [307], and does not have any serious adverse effects [305, 307]. In a recent double bind parallel group trial with over two hundred smokers, selegiline compliance was high and there was no evidence of an effect on

depressive symptoms [308]. When moclobemide is taken in similar doses to that used to treat depression, the major side-effect is insomnia [309].

Relative cost

Given their lack of efficacy, MAOIs are unlikely to be cost-effective treatment options for smoking cessation. Patch formulations of selegiline cost approximately US$ 600/month for treatment, which is substantially more than SSRIs [310].

Relative use

Given the lack of current evidence for their efficacy, it is unlikely that MAOIs will be licensed for smoking cessation. They are also not a first-line treatment option for depression.

Relative scope

If they had been shown to be effective, MAOIs would be appropriate for those with a co-morbid depression diagnosis and have fewer side effects than other antidepressants [86].

Relative ease of use

A transdermal form of selegiline, approved for the treatment of depression by the Food and Drug Administration, may be appropriate for those adverse to oral formulations [305]. Similar dosing profiles are required as for the other antidepressants, including bupropion [86].

3.4.7 Opioid antagonists

The promotion of opioid antagonists naltrexone, naloxone and buprenorphine was based on the idea that the reinforcing properties of nicotine may be mediated by the release of neurotransmitters which impact on the endogenous opiate system [311]. Naloxone is routinely administered to reverse the effects of narcotic overdose and naltrexone to blunt certain effects of narcotics, while buprenorphine reduces withdrawal symptoms following opioid discontinuation. A controlled-release formulation of naltrexone is approved to treat opioid and alcohol dependence in the US [312].

Relative efficacy

Research to date suggests that opioid antagonists do not promote smoking cessation, while results are mixed for effects on withdrawal symptoms, the hedonic effects of smoking, and cigarette consumption [311]. However, generally positive effects on post-cessation weight gain have been reported [313]. Concurrent use of buprenorphine and bupropion does not significantly increase abstinence from tobacco, opioids or cocaine relative to buprenorphine alone [314].

Relative safety

Common side effects of opioid antagonist administration include sedation, dizziness, nausea, constipation and vomiting. Physical dependence and addiction are also clinical concerns [315]. Less frequent side-effects include perceptual distortion, respiratory depression and myoclonus [316].

Relative cost

Opioid antagonist costs and availability vary widely in both developing and developed countries. The median cost of opioid antagonists as a percentage of GNP per capita per month are 36% for developing nations and 3% for developed nations [317]. Their cost effectiveness for smoking cessation is relatively unknown, however, given their lack of efficacy to date they are unlikely to be more cost-effective than first-line treatments.

Relative use

The current lack of evidence for their efficacy in relation to smoking cessation, and concerns over possible dependency and side effects means that they are unlikely to be licensed as smoking cessation aids.

Relative scope

Opioid antagonists may be particularly beneficial for those concurrently dependent on cigarettes and opioids (e.g. morphine, heroin and codeine), but are associated with a number of side effect.

Relative ease of use

Opioid antagonists have a similar dosage regimen to varenicline and bupropion. For example, one oral tablet of naltrexone costs between 25mg and 200mg per day [315]. However, many smokers are adverse to using oral medication and prefer transdermal product forms.

3.4.8 Selective cannabinoid type 1 receptor antagonists

Rimonabant and taranabant, selective cannabinoid-1 receptor antagonists, might restore imbalance in food intake and energy expenditure, which is often altered in smokers [232]. Although they were initially considered by medicines regulatory agencies for both weight loss and smoking cessation [318], rimonabant and taranabant were removed from the US market primarily due to adverse neuropsychiatric effects [319].

Relative efficacy

Rimonabant and taranabant appear to increase the chances of quitting and they may moderate weight gain, but evidence is inconclusive regarding long-term abstinence [320]. Clinical trials of Rimonabant which began in 2002, have also noted an increase in HDL cholesterol and decreased triglycerides [321].

Relative safety

In 2008 both rimonabant and taranabant were withdrawn by manufacturers, due to links with mental disorders and unacceptable side effects including digestive, nervous, psychiatric, skin and blood vessel disorders [322]. Other side-effects include headache, diarrhoea, insomnia and sinusitis.

Relative cost

There is no evidence for the cost-effectiveness of these products in relation to smoking cessation due to their removal from the market.

Relative use

Both rimonabant and taranabant have been withdrawn by manufacturers due to adverse side effects [322]. For weight control, rimonabant has been argued to be within the range of what is generally regarded as cost effective [323].

Relative scope

Rimonabant and taranabant may be suitable for those smokers wishing to prevent post-cessation weight gain, although side effects are likely to erode any benefits.

Relative ease of use

Rimonabant in previous studies has been used in a 20mg dose once per day [320, 322], which is similar to that recommended for other first-line treatments requiring a prescription. However, many smokers are adverse to using oral medication and prefer transdermal product forms.

3.4.9 Supplements (S-Adenosyl-L-Methionine (SAMe) and St John's wort)

Two supplements have been suggested as possible aids to smoking cessation as a consequence of their effects on biological compounds associated with the addictive effects of nicotine. The first, S-adenosyl-L-methionine (SAMe), is proposed to have anti-depressive properties by causing elevations in dopamine and noradrenaline levels and increases in 5-HT turnover [324]. The second, St John's Wort, is proposed to be a treatment for mild depression by a) inhibiting reuptake of norepinephrine, dopamine, and 5-HT; and b) having affinity for adenosine and GABA receptors [86, 325]. However, SAMe and St John's Wort's utility as treatments for depression have been questioned given the lack

of evidence for their efficacy relative to placebo [326], likely partially due to their poor bioavailability following oral administration [327-329].

Relative efficacy

Two small trials of St John's wort have failed to detect a significant effect on quit rates or withdrawal symptoms [330, 331]; although there may be some worthwhile benefits for preventing weight gain [330]. One trial of SAMe did not find significantly increased tobacco abstinence rates nor decreased nicotine withdrawal symptoms compared to placebo [332], and evidence is lacking for a dose response [86].

Relative safety

Treatment with SAMe up to 1,600mg/day for 6 weeks appears to be safe, well tolerated and with no serious side effects [333]. St John's Wort is not associated with adverse events, but is contraindicated for concurrent contraceptive use, and has mild side-effects including anxiety, dizziness, abdominal bloating and dry mouth [331, 334].

Relative cost

SAMe is relatively expensive compared to NRT, with prices for a 200mg tablet ranging from $0.75 to $1.25 [335]. St John's Wort is generally lower in price than other antidepressants such as bupropion [336], thus if it had been deemed effective may be a suitable option for developing countries.

Relative use

SAMEe and St John's Wort are both available over the counter; however, their lack of efficacy for smoking cessation means they are unlikely to increase overall use of treatments during smoking cessation.

Relative scope

These products may be suitable for those who are adverse to prescription pharmacotherapy and who are contraindicated for the other medications discussed in this review. They are also well tolerated and have fewer side-effects.

Relative ease of use

SAMe in clinical trials has been used in 400-mg four tablets a day formulations and St John's wort in 300-mg three tablets a day formulations [331, 332]. This may adversely affected treatment adherence relative to the first-line treatments which require one oral dose per day.

3.4.10 Other tricyclic antidepressants

Following the success of bupropion and nortriptyline other tricyclic antidepressants have been advocated, including doxepin and imipramine [86]. Doxepin's structure and general pharmacological properties are similar to imipramine and buproprion, but it also combines a sedative effect with antidepressant activity. Consequently, doxepin is generally used for those with sleep disturbances or depression associated with anxiety.

Relative efficacy

There are no long term studies of doxepin and imipramine, but short term trials suggest that imipramine does not significantly reduce cigarette consumption compared to a no-medication control [337]. Although doxepin improves cravings, two months sustained abstinence rates are similar to placebo [338].

Safety

Doxepin is generally well tolerated with side-effects which are similar in nature to those of other tricyclic antidepressants (e.g., dry mouth, drowsiness and constipation) [339]. Doxepin tends to cause fewer side-effects than imipramine [339, 340] and is well tolerated in the elderly with cardiovascular disease. However, although doxepin causes fewer cardiovascular side-effects than other anti-depressants, it has an intrinsic cardiotoxicity on overdosage [339].

Relative cost

Smoking cessation support with imipramine and doxepin would likely cost a similar amount as treatment with other antidepressants [341]. It has been suggested that doxepin tablets are one of the cheapest treatment options for depression [342].

Relative use

Although these products were once widely used as antidepressants, they have subsequently been replaced by newer antidepressant medications with better side effect profiles [86].

Relative scope

As with bupropion, tricyclic antidepressants are likely to be particularly useful for those suffering from depression. However, their side-effects would likely limit their use and many smokers may be adverse to using a drug associated with treating psychiatric conditions.

Relative ease of use

Tricyclic antidepressants have a similar dosing profile to varenicline and bupropion and the tricyclic antidepressant nortriptyline. However, many smokers are adverse to using oral medication to help them quit smoking.

4. Conclusion

National guidelines around the world recommend use of evidence-based aids for tobacco dependence to help smokers to quit and/or to reduce their cigarette consumption (e.g. England, America, Brazil, Uruguay and China)[343-346]. This includes a combination of behavioural support and pharmacotherapy [347, 348]. For example, in England, specialist stop smoking services, commissioned by local authorities, offer smokers face-to-face-counselling in addition to three first-line medications: NRT, bupropion or varenicline [347]. Although these have shown substantial efficacy, particularly when used in conjunction [349], calls have been made to increase their diversity [6, 350, 351].

This paper reviewed evidence for novel pharmacotherapies, contrasting them with the first-line treatments using six criteria (ESCUSE). Many of these medications are in early development and clinical trials have yet to be completed, thus conclusions of impact, efficacy and safety are limited. It does not appear that any single medication will serve as a panacea to effectively reduce smoking across the population, given that tobacco dependence reflects a complex interplay of neurobehavioral, genetic, environmental, and social factors [352].

Where evidence is available, cytisine appears to offer one of the best prospects for the future, having established safety and efficacy and being very inexpensive. Electronic cigarettes have become very popular in some countries but efficacy and long-term safety require further consideration. Nicotine vaccines and galenic formulations of varenicline could show promise if they respectively produce higher antibody levels and reduce side effects, while lorcaserin may prevent post-cessation weight gain. Several products report harm reduction benefits, including carvedilol and labetalol treatment, which are found to attenuate nicotine-induced increases in heart rate and blood pressure.

It has been argued that a major obstacle to the development of new smoking cessation and harm reduction medications is inefficient early clinical evaluations, with the vast majority of drugs failing to show efficacy for cessation after significant resources and time is wasted. This may be combated by more efficient designs (e.g. those which recruit only motivated smokers, have shorter out-come measures and use cross-over methods) [353]. Pharmaceutical companies also tend to focus research spending on the development of the next 'blockbuster drug'. Perhaps as researchers we should instead maintain focus on those products with proven safety and efficacy and assess how these can be used more widely and effectively. One way to increase effectiveness is through improved use and

adherence, for example via free provision or reimbursement schemes [354, 355] and tackling misperceptions about smoking cessation medication [356]. Many misperceptions arise from the information provided with smoking cessation medications, which by highlighting potential risks fails to educate that these pale by comparison to the real world documented risks of tobacco use [357]. Practice guidelines for nicotine dependence also only recommend that medication be integrated with behavioural support [19], while combined use of transdermal NRT and oral NRT, varenicline and NRT, and varenicline and bupropion, appear to result in significant benefits over sole use of any product [84, 358-362].

5. Compliance with Ethical Standards

5.1 Conflicts of interest

RW undertakes consultancy and research for and receives travel funds and hospitality from manufacturers of smoking cessation medications but does not, and will not take funds from EC manufacturers or the tobacco industry. RW and SM are honorary co-directors of the National Centre for Smoking Cessation and Training. RW is a Trustee of the stop-smoking charity, QUIT. EB has received unrestricted funding from Pfizer. LS has undertaken honoraria and expenses for attending and presenting at meetings and workshops from manufacturers of smoking cessation products. He has also received an unrestricted research grant from Pfizer. DMC declares no conflicts of interest.

Table 1: Overview of first-line treatments for smoking cessation according to ESCUSE

Drug	Efficacy	Safety	Cost	Use	Scope	Ease of use
NRT	Although licensed NRT products do not reproduce the rapid and high levels of nicotine that are obtained from cigarettes [363], clinical trials have shown that they typically double the chances of long-term abstinence [364]. NRT has also been demonstrated to be effective at a population level [350]. NRT products can also be combined to increase effectiveness e.g. slow acting transdermal product and fast acting non-transdermal product [32].	Many smokers perceive NRT to be less satisfying than smoking cigarettes, in part, as it fails to fully address the reinforcing effects of smoking e.g. the hand to mouth movement [232]. However, this does mean that NRT has low liability for abuse and a low dependence potential [365]. In clinical trials, the major side effects usually reported are hiccups (gum, sublingual tablet), gastrointestinal disturbances (gum), jaw pain (gum), dental problems (gum, sublingual tablet), nasal irritation (spray), and skin sensitivity (patch). Serious adverse events are sparse [364] and NRT does not appear to perpetuate cardiac disease [366-368]. However, questions have been raised about a possible excess of chest pains and heart palpitations among NRT users [369].	It has been estimated that the cost per week, although not cheap at £15 (US$ 22), is less than the £35 (US$ 51) that the average smoker will spend on cigarettes [370]. Moreover, many countries, including England, provide NRT on prescription at low cost or free of charge to disadvantaged sections of society, who have a higher prevalence of smoking and associated morbidities [371]. All cost-effective analyses generally find that NRT is highly cost-effective and this is reflected in NICE guidance [372].	Prior to the advent of NRT, few treatments were available to help smokers stop smoking, with most effort directed towards increasing the public awareness of the health implications of tobacco use [373]. Studies suggest that the introduction of novel NRT products may have grown the non-tobacco nicotine containing product market [55].	NRT has a list of contraindications such as heart disease, diabetes mellitus, active stomach ulcer, current use of asthma or depression medication, potential pregnancy and conditions relevant to the specific NRT product (e.g. patch: rashes or allergy to adhesives) [374-376].	Some NRT products are easier to use than others. For example, while the patch is discrete and activated by placing on the skin, smokers' often do not chew and park nicotine gum correctly [356]. Many smokers also report embarrassment of using the nicotine inhalator [377]. Nonetheless, NRT is available in many countries over-the-counter in local shopping outlets, and the large variety of products allows smokers to choose the most suitable options. The patch is applied for 16 hours and removed overnight or for 24 hours. Up to 15 pieces of gum and lozenges can be used per day. Patients should not exceed 12 inhalator cartridges of the 10 mg strength daily or 6 cartridges of the 15 mg strength daily. Patients can use 1 spray of the nasal spray in each nostril when the urge to smoke occurs, up to twice every hour for 16 hours daily
Bupropion	Bupropion significantly increases long-term cessation [86]. It appears to be equally effective for both men and women and those with and without a diagnosis of depression [86, 378]. Outside of clinical trials, bupropion has been shown to induce higher quit rates than NRT alone [379, 380]. There is also some evidence that it may be capable of minimising the associated weight gain of smoking cessation [381].	Although bupropion have been associated with mild side-effects, including dry mouth and insomnia; very few experience adverse effects [38, 382]. Following bupropions' launch in 2000, the media reported a number of deaths in, but post-marketing surveillance in the UK found only 60 fatal incidences over 2 years among 540,000 smokers; and most of these were caused by an underlying smoking-related disease [382]. Overall, the benefit of bupropion was deemed to outweigh any possible side-effects and so smoking cessation guidelines in both the UK and the US recommend it as a safe effective medication for those who wishes to use it [19, 383].	In the UK, the cost per life-time quitter for bupropion has been estimated at between £964 (US$ 1394) and £1,799 (US$ 2602), which is roughly equivalent to estimates in the US [384, 385]. Despite its higher cost, there is some evidence that bupropion is more cost-effective than NRT [386]; with an incremental cost per quality adjusted life year gained (QALY) of approximately one third less than that for NRT [387]	Prior to the introduction of bupropion the only pharmacotherapy available to help smokers quit was NRT. However, despite initial promise bupropion has failed to reach dominance, taking less than a 5% share of total prescribing for smoking cessation in England [388].	A reduced dose of bupropion may be required in elderly patients, people with diabetes and smokers with renal or hepatic impairment [389]. Bupropion is contraindicated in those who have experienced a recent myocardial infarction or arrhythmias or have severe liver disease [383]. Unlike for NRT, bupropion is not available over-the-counter and only some countries have licensed it as smoking cessation aid.	Treatment is usually started one to two weeks before a target stop date. The initial dose is 150mg which is taken daily for six days, increasing on day seven to 150mg twice daily [390]. Subsequently, most smokers use it for a further 7 to 12 weeks, but it can be taken for 6 months to a year [390]. Many smokers demonstrate poor adherence by taking inadequate doses [391]. Treatment discontinuation is also common due to side effects and medical concerns [392].
Varenicline	Studies have shown that varenicline is the most effective smoking cessation aid available [78, 393]. It is also the only drug which has proven long-term efficacy in smokers with chronic obstructive pulmonary disease [394, 395] and is efficacious for patients with psychiatric disorders [396]. The introduction of varenicline in the US appeared to coincide with a net overall increase in both aided and unaided attempts to quit smoking [40]; although a similar effect was not seen in the UK [57, 397]. Evidence is also emerging that greater benefits may be obtained through combination use with bupropion and that such concurrent therapy is well tolerated [362, 398].	Its safety in patients with cardiovascular disease has been questioned. Shortly after the drug was marketed, case reports emerged which linked its use to arrhythmias and myocardial infarctions [399]. Subsequent clinical trials reported a significantly increased risk of serious adverse cardiovascular events in users of varenicline; although more recent studies outside of the clinical setting failing to support the findings [72, 400-402]. Associations have also been drawn with possible neuropsychiatric events, although this may be explained, partially at least, by smoking itself. A large proportion of smokers have pre-existing psychiatric diagnoses, which may be exacerbated by the withdrawal process; whilst smoking-related conditions that often motivate a quit attempt, are themselves associated with an increased risk of neuropsychiatric events [70, 71, 403-406]. Moreover, population based studies and clinical trials have failed to identify any association between varenicline use and induced psychiatric conditions [407, 408].	Varenicline has been shown to be more cost-effective than either NRT or bupropion, though estimates vary greatly due to different methodologies [409-411]. The cost per additional quitter for varenicline is approximately £2,170 (US$ 3139) [412].	Varenicline has become the second most prescribed smoking pharmacotherapy in the UK after NRT [57]. However, it does not appear to have increased overall rates of prescribing for smoking cessation medication [69].	In the UK, varenicline has been licensed for use with all smokers except those with severe renal impairment, pregnant or breastfeeding smokers, and those under 18. There are some concerns regarding its association with cardiovascular events and neuropsychiatric events [70, 401]. This has resulted in regulatory bodies warning against its use in some patients. However, it is arguable that much of the reported behavioural and mood changes are a consequence not of the drug but nicotine withdrawal.	Generally, treatment begins 1 week before the quit date (1mg tablet twice or once daily). Subsequently, patients are given a further 12 weeks prescription. If the patient has not stopped smoking at this point, a further 12 weeks of treatment may be considered. However, adherence is often lower than for other pharmacotherapy, and as with bupropion, this is most likely due to concerns about side effects [392, 413, 414]. Varenilcine is also not available over-the-counter or on prescription in all countries.

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