FROM THE ANALYST'S COUCH

Smoking cessation drugs market

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Tobacco use is widely acknowledged as a serious threat to human health. It is a recognized risk factor in diseases such as cancer, coronary heart disease, stroke and chronic obstructive pulmonary disease. Currently, it is estimated that there are over 1.3 billion smokers worldwide, with prevalence averaging 33% of the adult population. According to the World Health Organization (WHO), around six million people die prematurely from tobacco-related disease each year, and this number could rise to more than eight million by 2030 (REFs 1,2). Nearly 80% of these deaths will occur among people in developing nations.

Tobacco dependence (nicotine addiction) begins when nicotine acts on nicotinic acetylcholine receptors (nAChRs) to release neurotransmitters such as dopamine, glutamate and GABA (γ-aminobutyric acid). Cessation of smoking leads to symptoms of nicotine withdrawal such as anxiety and irritability. To date, three types of medications have been widely licensed throughout the world for smoking cessation: nicotine replacement therapy (NRT), sustained-release bupropion (Zyban SR/Clorpax/Prexaton/Bupropion-RL; GlaxoSmithKline (GSK)) and varenicline (Champix/Chantix; Pfizer) (FIG. 1).

Nicotine replacement therapy

NRT is extensively used as a substitution for tobacco smoking. Currently, five US Food and Drug Administration (FDA)-approved medications — transdermal patches (NicoDerm; GSK), gums (Nicorette; GSK), lozenges (Commit; GSK), inhalers (Nicotrol; Pfizer) and nasal sprays (Nicotrol NS; Pfizer) — deliver nicotine in a form that does not involve the risks of smoking. A Cochrane systematic review found that all forms of NRT increased the chances of quitting by 50–70% compared to placebo or no treatment[3]. However, 93% of over-the-counter NRT users relapse and return to smoking within 6 months[4]. NRT becomes most effective when prescribed in conjunction with other medication and behavioural therapy.

Non-nicotine products

Two medicines that do not contain nicotine, bupropion and varenicline, are FDA-approved as smoking cessation products. Bupropion, an atypical antidepressant first approved in 1985, has been shown to approximately double the odds of quitting success. The drug's mode of action is unclear; however, it is thought to affect noradrenaline, dopamine and serotonin. Bupropion has also been approved for use in combination with NRTs for smoking cessation.

Varenicline, derived from cystine, is an α4β2 nAChR partial agonist and received FDA approval in 2006. It was shown that smokers using varenicline were three times more likely to succeed at long-term smoking cessation than those using no medication. Both bupropion and varenicline have side effects (mild to moderate nausea, and bupropion can cause insomnia) as well as several contraindications. In 2009, the FDA required both products to add new boxed warnings citing serious neuropsychiatric risks in patients using these drugs.

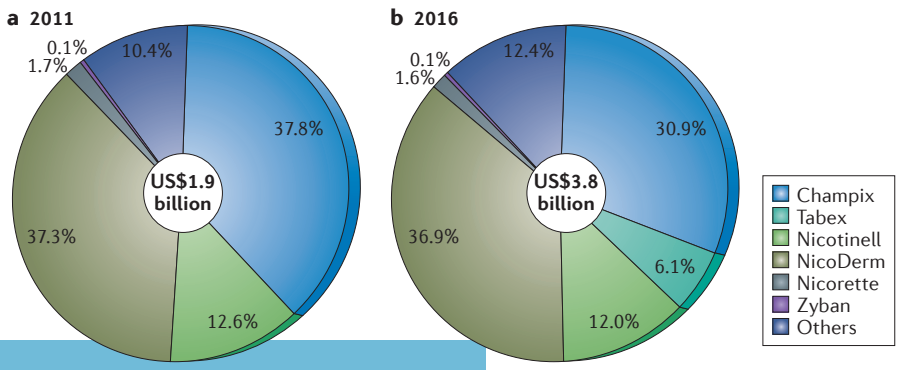

Figure 1 | **Leading smoking cessation brands in 2011 and 2016.** Source: Visiongain.

Second-line medications include clonidine (Catapres; Boehringer Ingelheim) and nortriptyline (Aventyl/Pamelor; produced by various manufacturers), and may be prescribed by clinicians if first-line pharmacotherapies are not effective. Nortriptyline, a second-generation tricyclic agent, and clonidine, an α_2-adrenergic receptor agonist, are generally prescribed for depression and high blood pressure, respectively; the FDA has not approved their use for smoking cessation.

Pipeline therapies

Smoking cessation therapies currently in development include candidates targeting the nAChRs, dopamine D3 receptor (DRD3), cannabinoid receptor 1 (CB_1R), monoamine oxidase B (MAOB) and other pathophysiological pathways implicated in nicotine addiction, as well as nicotine-derived therapeutic vaccines (TABLE 1).

Cytisine (Tabex; Sopharma/Extab), a plant alkaloid α4β2 nAChR partial agonist with a molecular structure similar to nicotine, is in Phase III development. It has been widely available as an anti-smoking aid in Eastern Europe; however, the drug is not approved in the United States, Japan or Western Europe. A range of nicotine-based pipeline candidates are in Phase II development, including NAL2762 (NAL Pharmaceuticals), an orally disolvable film (ODF) containing nicotine, and X-22 (22nd Century Group), a kit containing very low nicotine (VLN) cigarettes as a prescription smoking cessation aid.

MK0364 (Taranabant; Merck) is a CB_1R inverse agonist that acts by reducing appetite, increasing energy expenditure and fat oxidation. However, in a recent Phase II trial it did not improve smoking abstinence rates and was linked with high levels of adverse effects, mainly anxiety and depression. EVT 302 (Evotec) and selegiline (US National Institute on Drug Abuse) are MAOB inhibitors. However, EVT 302, an orally active, reversible and highly selective inhibitor, failed to demonstrate any major increase in cessation rates in a Phase II study. Selegiline, a selective and irreversible inhibitor, is being investigated in both oral and transdermal formulations for smoking cessation. Various small-scale ▸

trials demonstrated the effectiveness of the drug in reducing withdrawal symptoms and improving abstinence compared to placebo. However, in a Phase II study of heavy smokers, oral administration of selegiline failed to increase cessation rates.

Meclizine (Duke University/Philip Morris USA), an antihistamine used for motion sickness, is in Phase II development for ad lib smoking and as a combination treatment with a nicotine patch. D-cycloserine (Boston University), a partial NMDA (*N*-methyl-D-aspartate) receptor agonist, is also in Phase II trials. Other late-phase agents include GSK598809 (GSK), a DRD3 antagonist, and two opioid receptor antagonists: nalmefene (Somaxon Pharmaceuticals) and naltrexone (University of Chicago) (TABLE 1).

One novel approach is to vaccinate smokers against nicotine. The premise is that vaccine-induced antibodies should bind to nicotine in the blood and prevent it from reaching the nAChRs in the brain, thereby breaking the addiction cycle. However, NicVAX (Nabi Biopharmaceuticals/GSK), the first such vaccine to reach Phase III testing, failed to meet the primary end point, with cessation rates roughly the same (about 11%) as placebo. However, a study of NicVAX in combination with varenicline is ongoing. An interim analysis of the vaccine candidate NIC-002 (Cytos, Phase II) showed that it did not achieve the primary end point of smoking cessation. TA-NIC (Celtic Pharmaceuticals) and Niccine (Independent Pharmaceutica) are other nicotine-derived therapeutic vaccines that are in Phase II development. Despite early setbacks, vaccination offers the prospect of a multifaceted approach to treat nicotine addiction as a stand-alone therapy or in conjunction with non-nicotine medicines and behavioural intervention.

Table 1 | **Selected treatments in clinical development for smoking cessation**

Product	Developers	Mechanism of action	Development stage
Tabex (cytisine)	Sopharma/Extab	nAChR partial agonist	Phase III
NicVAX (3-aminomethyl nicotine hapten) plus Champix (varenicline)	Nabi Biopharmaceuticals	Therapeutic vaccine combination product	Phase II
Taranabant (MK0364)	Merck & Co.	CB_1R antagonist and/or inverse agonist	Phase II
EVT 302	Evotec	MAOB inhibitor	Phase II
Selegiline	NIDA	MAOB inhibitor	Phase II
TA-NIC (nicotine butyric acid covalently linked to recombinant cholera toxin B)	Celtic Pharmaceuticals	Therapeutic vaccine	Phase II
Niccine	Independent Pharmaceutica	Therapeutic vaccine	Phase II
NIC-002	Cytos Biotechnology/ Novartis	Therapeutic vaccine	Phase II
D-cycloserine	Boston University	NMDA receptor agonist (also used as broad-spectrum antibiotic)	Phase II
GSK598809	GlaxoSmithKline	DRD3 antagonist	Phase II
Nalmefene	Somaxon Pharmaceuticals	Opioid receptor antagonist	Phase II
Naltrexone (naltrexone HCl)	University of Chicago	Opioid receptor antagonist	Phase II
NAL2762 (nicotine ODF)	NAL Pharmaceuticals	nAChR ligand	Phase II
Meclizine (meclizine hydrochloride)	Duke University/ Philip Morris USA	Antihistamine	Phase II
X-22 (nicotine)	22nd Century Group	Kit of VLN cigarettes	Phase IIb

CB_1R, cannabinoid 1 receptor; DRD3, dopamine D3 receptor; MAO, monoamine oxidase; nAChR, nicotinic acetylcholine receptor; NIDA, US National Institute on Drug Abuse; NMDA, *N*-methyl-D-aspartate; ODF, orally dissolvable film; VLN, very low nicotine. Sources: ClinicalTrials.gov website, scientific literature and company reports.

Market outlook

The current market for smoking cessation therapies is estimated to be worth US$1.9 billion a year and is expected to reach $2.3 billion by 2016 (compound annual growth rate: 3.8%; 2011–2016)[1]. The market is dominated by NRT products, claiming about 57% of the total market share. With only two non-nicotine-based prescription medications currently approved, Pfizer's Chantix/Champix brand leads the market with a share of 37.8%. Growth in the global smoking cessation market will largely depend on the approval of safer and more effective drugs with minimal side effects. Tabex is an inexpensive drug and has shown promise; when approved, it will therefore pose a strong challenge to Champix.

Although the prevalence of smoking has decreased in the past decade, there is a lack of a significant decline. There are around 45 million smokers in the United States alone, with more than 70% reporting a desire to quit. On average, a smoker will make multiple attempts to quit during their lifetime. Also, over 75% of patients receiving cessation treatment relapse to smoking within the first year. As tobacco use continues to remain a serious public health problem, an urgent need persists for a greater awareness on smoking cessation and better drug therapies to treat nicotine dependence.

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Competing interests statements
The authors declare no competing financial interests.