Review

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# Improved treatment of nicotine addiction and emerging pulmonary drug delivery

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**ABSTRACT: Nicotine addiction remains the leading cause of death and disease in developed and developing nations and a major cause of mortality around the world. Currently, nicotine replacement therapies (NRTs), bupropion, and varenicline are approved by the regulatory agencies as first-line treatments for nicotine addiction. Emerging evidence indicates that varenicline and bupropion have some therapeutic limitations for treating nicotine addiction with oral route of administration. Thus, continued investigation of innovative drug delivery for nicotine addiction remains a critical priority. This review will discuss some novel strategies and future directions for pulmonary drug delivery, an emerging route of administration for smoking cessation. It is anticipated that the advancement of knowledge on pulmonary drug delivery will provide better management for nicotine addiction and other addictive disorders.**

***Keywords:*** Nicotine addiction, bupropion, varenicline, nicotinic receptor, pulmonary drug delivery, dry powder inhaler (DPI), metered dose inhaler (MDI), nebulizer

## 1. Introduction

Tobacco smoking and nicotine addiction is a growing public health problem in the developing and developed world. The World Health Organization (WHO) estimates that about 30% of the adult male global population smokes (*1*). It is estimated that each year tobacco smoking accounts for about 3 million deaths worldwide. Unless the current trends are reversed, by the year 2030, this figure will be increased to 10 million deaths every year. Seventy percent of these deaths are predicted to be in developing nations. In the USA alone, tobacco smoking causes 440,000 deaths annually (*2*). Approximately, 50% of long-term tobacco smokers die prematurely from adverse effects of smoking, including cancer, cardiovascular disease, lung disease or other illness (*3*). The risk of tobacco smoking can be reduced significantly by smoking cessation with multiple strategies including pharmacotherapy. Current pharmacotherapies (Table 1) include nicotine replacement therapy (NRT) in the form of gum, transdermal patch, sublingual tablet, nasal spray, and vapor inhaler formulations; however, each therapy has its advantages as well as some significant drawbacks (details in the section 5.1.). There are two non-nicotine based medications which have been approved by the US Food and Drug Administration which are bupropion (Zyban) and varenicline (Chantix) (*4-6*). Recent data suggest that varenicline and bupropion have some therapeutic limitations or adverse effects for treating nicotine addiction with current delivery system. Like other brain disorders (Table 2), continued investigation of innovative drug delivery for nicotine dependence remains a critical priority. In this review, we will discuss novel strategies and future directions for smoking cessation using a suitable inhaler for deep lung delivery of nicotine, an emerging route of drug administration. The currently available nicotine inhaler delivers nicotine into the mouth for buccal absorption and there is no ideal inhaler to deliver nicotine into the deep lung. The pulmonary route of nicotine delivery would be expected to mimic the effects of tobacco smoking and would significantly reduce cravings and withdrawal symptoms. It is anticipated that the advancement of knowledge on pulmonary drug delivery will provide novel therapeutic formulations for better management of nicotine addicted population. Improvement of nicotine addiction treatment depends on the novel pharmacotherapeutic approaches, including new drugs or new formulation of current drugs and/or novel delivery technique, like deep lung delivery, which is discussed in the following sections.

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**Table 1. Currently approved medications for smoking cessation (*4,57*)**

| Pharmacotherapy | Common side effects | Delivery methods |
|---|---|---|
| NRT* | Skin reaction, insomnia, irritation of mouth and throat | Oral, nasal, skin, nicotine cartridges in an inhaler, pMDI |
| Bupropion (Zyban®) | Insomnia, dry mouth, suicide ideation | Oral |
| Varencline (Chantix®) | Headache, mood changes, insomnia, constipation, suicide ideation | Oral |

* NRT: nicotine replacement therapy.

**Table 2. Drugs administered as aerosols against smoking cessation and other neurological diseases**

| Active drugs | Indication | Formulation | Delivery system | References |
|---|---|---|---|---|
| Nicotine | Smoking cessation | Aqueous solution | MDI (AERx Essence®) | (*72,73*) |
| Nicotine | Smoking cessation | Suspension | MDI | (*70,71,83*) |
| Nicotine | Smoking cessation | Micronized powder | DPI | (*67*) |
| Nicotrol®, Nicorette® (Nicotine) | Smoking cessation | Nicotine cartridge/Liquid | DPI & MDI | (*64,68*) |
| Dihydroergotamine mesylate | Migraine, Vascular cephalgia | HFA 134a based suspension | MDI | (*84*) |
| Ergotamine tartrate | Migraine, Vascular cephalgia | Suspension | Unavailable | (*50*) |
| Detorelix | Migraine, Vascular cephalgia | Suspension of liposomal drugs | Intratracheal (*i.t.*) instillation | (*85*) |
| Dopamine D-1 agonist, ABT-431 | Parkinson's disease | HFA based suspension | MDI (AERx) | (*86,87*) |
| L-Dopa | Parkinson's disease | Micronized powder | Alkermes AIR/DPI | (*52,88*) |
| Dopamine agonist | Parkinson's disease | Suspension in propellant and poloxamer | MDI | (*89*) |

MDI: metered dose inhaler; HFC is hydrofluoro alkane; AERx is a DPI device that deliver aerosolized drugs from a dosage form that consists of liquid drug formulation.

## 2. Pulmonary delivery technology

Aerosol delivery of drugs, formulated as liquid solutions, suspensions, emulsions, or micronized dry powders, are aerosolized *via* some commonly used different types of delivery devices *i.e.*, nebulizers, metered dose inhaler (MDI), and dry powder inhaler (DPI). Nebulizers deliver large volumes of drug solutions or suspensions and are used for those drugs which are difficult to be formulated into pressurized metered dose inhalers (pMDIs) or DPIs. Nebulizers are suitable for drugs with high dose and little patient co-ordination or skill; however, treatment using nebulizer is time consuming and less efficient, resulting in the waste of active medicaments. They are not portable devices and have been limited to the treatment of hospitalized patients only.

Metered dose inhalers/pMDIs are the most commonly used delivery devices (Figure 1), which deliver drug. In this delivery method, drug is either dissolved or suspended in liquefied propellents. The propellents used in pMDI formulations are liquefied gases of chloroflurocarbons (CFC), which are not environmental friendly. This is the reason why currently hydrofluoroalkanes (HFAs), which have no remarkable effects on the ozone layers, are used in the formulation for MDIs. On spraying, drug formulation with propellants is expelled and aerosolized (Figure 1). Although pMDIs are widely used in respiratory drug delivery, some problems have been associated with these devices, including the need for coordination of inspiratory inhalation with valve actuation and the use of a propellant, which has possible adverse effects on the stratospheric ozone layer.

In addition, pMDIs have some other disadvantages such as oropharyngeal deposition of drugs. On actuation, the particles aerosolized from the MDIs have a high velocity, which exceeds the patients' inspiratory force, therefore, a large number of particles deposit onto the oropharyngeal areas. Thus a small fraction of drug deposits into the patients lungs due to a lack of co-ordination between actuation and inhalation (*7*). To overcome this difficulty several inhalation aids like spacers incorporated with MDIs have been developed (*8*) to improve the delivery; however, bacterial contamination of spacer devices are very common if the devices are not cleaned and dried appropriately (*9*).

Dry powder inhalation formulations contain the drug in a powder form and the drug particles (< 5 μm) are blended with a suitable large carrier (*i.e.*, lactose) to improve flow properties and dose uniformity (*10*) and drug powders are delivered into the deep lung *via* DPI devices (Figure 2). Powder de-agglomeration and aerosolisation from these formulations are achieved by the mechanical force provided by the device and patient's inspiratory airflow, which needs to be sufficient to create an aerosol containing respirable drug particles for lung deposition. Good flow properties of the formulation are necessary to ensure accurate dose metering of the drug. Advantages of DPI over other inhaler systems (pMDIs) are independence of breathing co-ordination with dose actuation, the absence of propellants, low innate initial velocity of particles (reducing inertial impaction at the back of the throat), and solid state drug stability. Drug dispersion from the powder formulation can be enhanced by the addition of fine excipients in the formulation (*11,12*). Drug particle size and powder formulation, breathing patterns, and complex physiology of respiratory

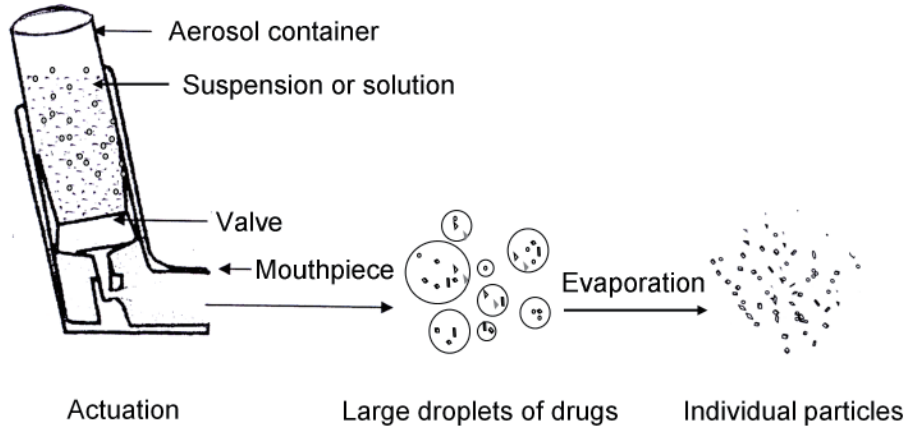


**Figure 1. Schematic diagram of aerosol delivery of drugs from pMDI.** Modified form Dalby *et al*. (*94*).

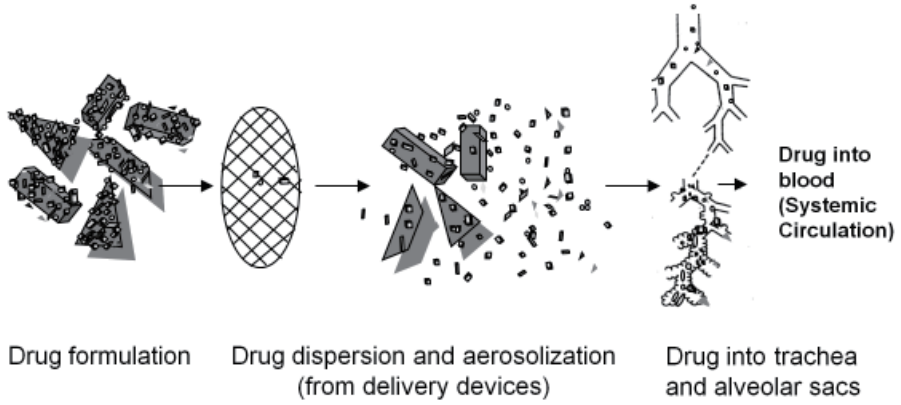


**Figure 2. Schematic diagram of the pulmonary delivery of drugs from DPI formulation.** The formulation consists of micronized drugs adhered on the surface of large carrier particles. Drug particles detached from the surface of large carriers and deposits into the patients airways by inhalation.

tract are major factors affecting delivery of drugs into the deep lung. DPIs are highly portable, breath activated, and relatively less expensive. Since drugs are kept in solid state in DPIs, they exhibit high physicochemical stability of drugs particularly proteins and peptides. In DPI formulation the device is an important factor in achieving adequate delivery of inhaled drug to lungs. The device must provide an environment where the drug can maintain its physicochemical stability and produce reproducible drug dosing.

On inhalation, drugs are dispersed and delivered into deep lungs. To achieve a desired therapeutic effect from aerosols, an adequate amount of drug must reach the alveolar sacs of the respiratory airways. The dynamic behavior of aerosol particles is governed by the laws of aerosol kinetics (*13*). The dominant mechanisms of depositing aerosol particles into the respiratory tract include inertial impaction, sedimentation (gravitational deposition), Brownian diffusion, interception, and electrostatic precipitation (*14*). The distribution of the inhaled drug particles in the lung depends on the characteristics of the inhaled particles, such as drug particle diameter, mass, shape, density and hygroscopicity, the physiology of the respiratory tract, and breathing patterns of the patients (*15-17*). Inertial impaction and sedimentation are the most important for large particle deposition (1 μm < MMAD < 10 μm). Large particles (> 5 μm) with high velocity (due to higher mass) are mainly deposited by impaction (*18*). Particles of smaller size (0.5-3.0 μm), which have tendency to escape from deposition by inertial impaction, may be deposited by sedimentation. Deposition of small particles by sedimentation mainly occurs in the smaller airways and alveolar regions and increased sedimentation is observed during breath-holding or slow steady breathing (*18*). Deposition of particles less than 0.5 μm occurs in the lower airway of lungs by diffusion due to Brownian movement. Generally, the deposition of particles larger than 1.0 μm is dominated by inertial impaction and particles smaller than 0.1 μm are deposited by diffusion. Both sedimentation and diffusion are important for the particle size ranging between 0.1-1.0 μm (*19*). The maximum pulmonary deposition of particles of 1.5-2.5 μm and 2.5-4 μm diameters occurred with and without breath holding, respectively. However, rapid breathing showed maximum deposition of particles between 1.5-2 μm in the tracheobronchial region with breath holding and particles between 2-3 μm deposited in the pulmonary

region without breath holding (*15*). Therefore, slow inhalation is desirable to obtain maximum deposition of aerosol particles in the lower airways of lung. Although particles less than 1 μm have challenging dispersion behavior due to the strength of the inter-particle forces, inhaled nanoparticles or nanoagglomerates of various drugs showed better dispersion (*20-24*), rapid absorption (*25*), and avoidance of mucociliary clearance (*26*). Recently, a formulation containing carrier lactose and salbutamol sulphate nanoparticles, which demonstrated a 2- to 3-fold increase in total lung deposition compared to a formulation containing the same drug as micronized form (*20*) has been reported.

Electrostatic charges may be generated in a DPI on particles of an aerosol and a charged particle may induce an image charge of opposite polarity on the airway walls during inhalation. This image charge attracts the particle which is subsequently deposited by electrostatic precipitation (*18,27*). Only fibrous particles are believed to be deposited by this mechanism, therefore, this mechanism may not be significant for DPI formulations.

**3. Pulmonary delivery of various drugs**

Currently, local delivery of medicaments to the alveoli of lungs from both DPIs and pMDIs are mainly used for the treatment of lung disorders including asthma and chronic obstructive pulmonary disorders (COPD) and a limited number of therapeutic compounds such as β-adrenoceptor agonist, muscarinic agonist, corticosteroids, and mast cell stabilizers are available. Recently certain combinations of drugs are also formulated due to a synergistic therapeutic benefit. Zanamavir, an antiviral agent has been introduced in the market as an aerosol product for the treatment of influenza (*28*). Aerosol delivery of recombinant human deoxyribonuclease (rhDNase) and tobramycin are available as nebulizer for the treatment of cystic fibrosis (*28,29*). The very first approved aerosol delivery of insulin as DPI formulation (Exubera®, Pfizer) was introduced in the market, however, the production has been discontinued from market because the sales of this product were disappointing as the product failed to gain acceptance of patients and physicians. The manufacturer failed to demonstrate the clinical benefits of the inhaled insulin over the currently available self-injection insulin products to the doctors and patients. Although the DPI product is stable (compared to the liquid injectable product) and easy to use; however, due to the higher cost of Exubera®, clumsy design of the device and poor marketing are also responsible for this breakdown.

Using DPI technique respiratory delivery of other potent drugs or other agents, such as hormone (*30*), antibiotics (*31,32*), drugs for Parkinson's disease (*33*), gene delivery (*34,35*), vaccine delivery (*36-38*), antituberculosis (*39,40*), antihypertensive nifedipine (*21*), anticoagulant heparin (*41*), drugs for sexual dysfunction (*42*), opioids (fentanyl) for cancer pain (*43-45*), and atropine sulphate nanoparticle as an antidote for organophosphorus poisoning with better bioavailability have been reported (*46*). The inhaled dry powders of levodopa showed to produce a therapeutic effect within 10 min of administration for the treatment of Parkinson's disease (*47*). Using a mouse model, deep lung delivery of poorly water soluble drug, ibuprofen nanoparticle showed 3-5 orders of magnitude less dose than that required for oral administration of the drug to achieve the same analgesic effect (*48*). Deep lung delivery of various drugs has been investigated and the pulmonary route has been found to be more effective compared to those of other routes. Aerosol delivery offers the greatest potential to delivery drugs into the lower airway of lungs of a wide range of molecules for systemic diseases.

**4. Pharmacokinetics of some inhaled drugs**

Very little is known about the pharmacokinetics of inhaled drugs. Recently, the bioavailability of levonorgestrel after pulmonary and oral administration has been investigated and pulmonary delivery of liposome encapsulated levonorgestrel produced prolonged effective concentration of the drug in the plasma over a period of 16-60 h with reduced side effects compared to that of orally administered drug (*49*). Higher plasma concentration of ergotamine tartrate was found when delivered *via* pulmonary route compared to that of orally administered tablet (*50*). This study revealed the superiority of inhaled route to the oral route of drug delivery. In another study, inhaled L-dopa produced at least 2-fold fewer doses compared to that of oral dose (*51*). Using a rat model, lung delivery of L-dopa dry powder formulation, developed by Alkerme's Advanced Inhalation Research (AIR), showed rapid and higher plasma levels ($C_{max}$, 4.8 ± 1.10 mg/mL in 2 min) compared to that of oral administration where the drug produced delayed and lower plasma level ($C_{max}$, 1.8 ± 0.40 mg/mL) in 30 min (*52*).

Deep lung delivery of Ergotamine tartrate (ET) *via* an inhaler (Medihaler®) produced 9-fold higher peak plasma concentration ($C_{max}$, 1,109 pg/mL at 4 min) compared to that of sublingual ET formulation ($C_{max}$, 134.0 pg/mL at 37 min) (*53*). Inhaled testosterone in postmenopausal women delivered by AREx (a novel handheld aerosol delivery system) produced a dose dependent increase in plasma drug concentration (*54*). After administering the maximum dose of 3.0 mg, plasma concentration ($C_{max}$) of free testosterone was increased from 0.6 nmol/L to a maximum level of 62.6 nmol/L achieved within 1-2 min after dosing. The authors demonstrated that the administration of inhaled testosterone was safe and no adverse effects related to the treatment occurred. Inhalation route can be an alternative route with safety profile to consider for many therapeutic agents (*55*). Thus the lung delivery of drugs has a lot of potential in managing various diseases with excellent pharmacokinetic profiles.

## 5. Medications for smoking cessation

### 5.1. *Nicotine replacement therapy*

Nicotine replacement therapy (NRT) may facilitate smoking cessation in several ways. The primary action is believed to be the relief of craving and withdrawal symptoms when a person stops tobacco use (*56*). The second critical effect of NRT is being positive reinforcement. The third possible mechanism of benefit has been suggested to be the potential for nicotine based medications to desensitize brain nicotinic acetylcholine receptors (nAChRs). A desensitized state of nAChRs such as alpha4beta2 subtype and/or other subtypes may cause in reduced receptor responsiveness to endogenously released acetylcholine which may be relevant to general mood stabilizing effect (*57*). Currently, NRT is available in 5 different formulations with different pharmacokinetic profiles, *i.e.,* chewing gum, lozenges, sublingual tablets, transdermal patch, and/or nasal spray inhale. The gum is available in two doses (2 or 4 mg) and the amount of drug absorbed from nicotine gum is much lower (~50%) than nicotine content in the formulation. With regards to the lozenges chewing is not required but like gum, nicotine from this preparation is absorbed very slowly through the buccal mucosa. A significant amount of nicotine is swallowed when using sublingual tablets, gum or lozenges and undergoes hepatic first pass metabolism and thus reduced bioavailability (20-45%) (*58,59*). The transdermal patch is much easier to use; however, the rate of nicotine delivery from this formulation is very slow and has an initial lag time of about 1 h before nicotine appears in the blood stream and a very slow rise (2-6 h) (*60*). Nicotine absorption from sublingual tablets are somewhat higher than that of gum; however, efficacy rates appeared to be consistent with gum and lozenge preparation (*61*). Absorption of nicotine from capsules or solutions is not promising and peak plasma concentrations are achieved in about 1 h after oral administration (*59,62*). Nicotine is ionized at low pH (stomach) and thus poorly absorbed from the stomach but it is well absorbed from intestine due to alkaline pH. The pharmacokinetics of currently available nicotine dosage forms are presented in Table 3, which indicates that the absorption of nicotine from orally administered formulations is slower and peak plasma concentrations are gradual compared to that of smoking. No significant difference in efficacy has been shown between formulations (*3*). Nicotine absorption from nasal spray is very rapid ($C_{max}$ 8.6-10.5 ng/mL at 2.5-5 min) (*63*) compared to that of gum; however, it has some unavoidable drawbacks like burning nose and throat, watery eyes, runny nose, sneezing, and coughing (*64*), which limit its application in smoking cessation. The nicotine vapor inhaler (inhaled by mouth) containing nicotine cartridge (10 mg each) deliver nicotine more into the oral cavity, stomach and very little into lungs (*65*). This is not a real inhaler that delivers drug into the deep lungs for better absorption. In addition, the nicotine delivery from this type of inhaler is temperature dependent (to vaporize the nicotine) and the inhaler is required to be kept warm before inhalation. From the above discussion, it is evident that each of the above mentioned nicotine based therapy has its advantages as well as some unavoidable limitations.

Although these products are alternatives of the nicotine associated with tobacco consumption, none of these found to produce rapid absorption and quick onset of action that can be achieved with cigarette. It is assumed that these products do not show the ability to effectively relief the craving for cigarettes associated with nicotine withdrawal. Therefore, this intense craving drives smokers back to cigarettes. New delivery method such as pulmonary drug delivery may enhance the efficacy of some NRT formulations. The pulmonary route is known as one of the efficient methods of delivering drugs to the body due to large surface area of the pulmonary alveoli, small airways, and dissolution of nicotine products in the fluid of pH 7.4 in the lungs facilitates transfer across membrane. A unique inhaler (DPI or MDI) would deliver nicotine to the lung in a manner comparable to nicotine intake through smoking. It is anticipated that this new method like lung delivery of nicotine would reduce background cravings and withdrawal symptoms for rapid relief of cravings (*57,66*). Thus pulmonary drug delivery technology may revolutionize the effective treatment by right NRT formulations and the following section is dedicated to demonstrate the current status and future direction of developing inhalable nicotine formulation.

**Table 3. Pharmacokinetics (average values) of different dosage forms of Nicotine products**

| Dosage forms and administration | $C_{max}$ (ng/mL) | $T_{max}$ | Ref. |
|---|---|---|---|
| Smoking | | | |
| 1.1 mg/cigarette | 25.9 | 2.0 min | (*71*) |
| 0.9 mg/cigarette | 38.9 | 4.0 min | (*90*) |
| MDI | | | (*71*) |
| 50 µg /puff (0.5 mg dose) | 12.5 | 6.0 min | |
| 100 µg /puff (1.0 mg dose) | 9.4 | 5.0 min | |
| Vapor Inhaler (10 mg cartridge) | 8.1 | 30 min | (*91*) |
| Nasal spray (2.0 mg) | 8.6-10.5 | 2.5-5 min | (*63*) |
| Nicotine vapor inhaler (1.1 mg) | 5.8 | 10 min | (*90*) |
| Nicotine Gum (2.0 mg) | 6-9 | 30 min | (*92*) |
| Logenze | | | (*93*) |
| 2.0 mg | 4.4 | 60 min | |
| 4.0 mg | 10.8 | 66 min | |
| Transdermal patch | | | (*60*) |
| 15 mg/16 h | 11.9 | 6.5 h | |
| 21.0 mg/24 h (Novartis) | 17.0 | 10 h | |
| 21.0 mg/24 h (Alza) | 21.9 | 3.8 h | |
| Oral solution 2.0 mg | 4.7 | 52 min | (*62*) |
| Oral capsules 3-4 mg | 6-8 | 90 min | (*59*) |
| Sublingual tablet 2.0 mg | 13.2 | 20 min | (*61*) |

5.2. *Deep lung delivery of nicotine*

No DPI/MDI formulations for pulmonary delivery of nicotine have been approved yet for the management of nicotine addiction. Only two products, *i.e*., Nicotrol® and Nicorette® Inhalers (Pfizer) of nicotine are available as nicotine vapor inhaler; however, these devices deliver nicotine into buccal areas, not into the deep lungs, resulting in lowering plasma maximum concentration and delayed time to reach maximum concentration. In 1997, Rose *et al.*, patented a DPI formulation of nicotine bitartrate with lactose powders for lung delivery with a view to manage smoking cessation; however, no further details are accessible (*67*). In an early study, a nicotine pMDI formulation containing nicotine in ethanol with hydrofluoroalkane (HFA), produces a microaerosol of fine droplet size that mimics the nicotine delivered *via* tobacco smoke (*68*). The author emphasized the nicotine pMDI offered safer delivery compared to that of smoked tobacco where heat, carcinogens, and carbon monoxide produce various adverse effects. Delivery of nicotine to the deep lung was comparable to cigarette smoking and this method showed to reduce cravings and nicotine withdrawal symptoms (*69*). A breath-activated MDI nicotine formulation, that produced a fine particle dose (FPD) up to 60%, would rapidly produce maximum plasma concentration to reduce smoking urges (*70*). This type of nicotine delivery is encouraging and suitable for relieving nicotine addiction; however, no further details are available. Very recently, using a large spacer with MDI lung delivery of nicotine produced a median maximum plasma concentration, which was about 50% of the amount that was obtained by smoking a cigarette (*71*). This formulation produced higher peak plasma levels and was achieved rapidly compared to those of many current forms of nicotine replacement therapy. In addition, inhaled MDI formulation showed self-satisfaction and reduce urge to smoke similar to a cigarette. Gonda *et al*., delivered clean nicotine aqueous solution to the deep lung for tobacco smoking cessation treatment using a promising device, AERx Essence® inhaler (*72,73*) and produced a rapid and dose proportional increase in plasma nicotine concentration within 1 min (data not accessible). Although nicotine was eliminated rapidly from the blood stream, prolonged craving reduction was observed without administering another dose. The craving reduction could be due to changes in brain nicotinic receptor regulation and neuroadaptation associated with brain reward circuitry (*3-5*). These studies suggested that deep lung delivery of nicotine using inhaler devices with better formulation would be an effective way to eliminate the craving for cigarettes and other tobacco products.

Nicotine absorption *via* lung from smoking is very rapid and currently available nicotine products (Table 3) deliver nicotine more slowly compared to that of smoking, which indicates that the pulmonary delivery is advantageous over other routes. The typical steady-state plasma concentrations of nicotine from gum, inhaler, sublingual tablets, and nasal spray is in the range of 5-15 ng/mL and from nicotine patches (according to the design and dose of nicotine in patches) in the range of 10-20 ng/mL (Table 3). Administration of nicotine capsules or solution found to produce peaks plasma concentrations in about 1 h (*59,62*). The absorption of nicotine from gum is not fast and frequent dosing is required to achieve good absorption from the oral mucosa to achieve peak plasma levels of nicotine. Nicotine absorption from transdermal patch is very slow and plasma concentration rises gradually over 6-10 h (depending on the type of product). The nicotine absorption from nasal spray was rapid and peak plasma concentration achieved within 5 min after administration (*63*) with a high individual variability. Hence, from the table it is evident that pulmonary delivery confirmed promising outcome compared to those of currently available non-inhaled nicotine products (tablets, capsules, nasal spray, gums, *etc.*).

5.3. *Non-nicotine based medications*

Currently there are some non-nicotine based drugs, such as bupropion (Zyban®) and varenicline (Chantix®) available for the treatment of nicotine addiction and these drugs are considered better for the management of smoking cessation (*74-78*). Bupropion was originally marketed as an antidepressant agent but the effect on nicotine addiction appears to be separate from its antidepressant effect. It is an inhibitor of brain dopamine uptake process. In addition, bupropion in low doses can block brain nAChR function (*74*). The blockade of nAChRs function could decrease positive reinforcement effects in addicted populations (*75*). This drug is extensively metabolized by liver enzyme ($t_{1/2}$ approximately 21 h). The prolonged absorption of this drug was observed from sustained release and extended release formulations, with $T_{max}$ values of 3.0 and 5.0 h, respectively compared to that of immediate release ($T_{max}$ 1.5 h); however, $C_{max}$ and AUC values found to increase proportionately with dose for all of these formulation (*76*). It is important to note that the pharmacokinetic profile of this drug is affected by age, sex, smoking, and renal and liver of the consumers. This drug is administered as a sustained-release formulation because of the major adverse effect – generalized seizures, which follow up high peak plasma concentration of that drug. The commonly observed side effect of bupropion is insomnia, but its occurrence can be reduced by taking the medication earlier in the day. Apart from insomnia, the most frequent effects are mouth dryness and nausea. It is contraindicated in patients who are suffering from seizure disorders. The dose is usually 150 mg/day for the first 3 days and then 150 mg twice daily. Bupropion is useful either as a monotherapy or in combination

with NRT. Combination with NRT seems to be safe but there is a lack of studies demonstrating an increased long-term quit rate (*3,4*). Evidence suggests that bupropion blocks brain dopamine and/or norepinephrine transporters for its antidepressant effect (*3*). Recently, it was found that bupropion with a very low concentration may act as an antagonist at certain subtype of nicotinic receptors (*3,5*). Whether this pharmacological property of bupropion may account for smoking cessation effect remains to be confirmed. Although pulmonary delivery of this drug has not been studied yet, this mode of delivery system would be expected to be more efficacious in terms of better pharmacokinetic (PK) and pharmacodynamic (PD) profiles for a better therapeutic outcome and effectiveness in the management of nicotine addiction resulting in enhancing the quit rate.

Varenicline, the latest drug included in the list of non-nicotine medication as a potential drug for the management of smoking cessation. The drug was developed as a cytisine derivative to increase oral bioavailability and improve brain penetration (*77*). Varenicline is a partial agonist at nAChRs with higher affinity for brain alpha4beta2 compared to other subtypes such as α7 (*77*). Preclinical and clinical research has shown that varenicline produces less of a response than that of nicotine (30 to 60%) that would counteract the low brain dopamine levels occurred in the absence of nicotine during smoking cessation attempts (*78*). Thus the drug removes symptoms of craving and withdrawal. Overall, varenicline acts like a functional antagonist, reducing nicotine-induced brain dopaminergic activation (*3,4*). Moreover, the efficacy of varenicline was found to be higher than that of bupropion in preclinical and clinical studies (*4*). Several side effects with varenicline, such as nausea, vomiting, and vivid dreams have been reported in addicted populations. There have been reports about depression, suicidal thoughts, suicides, and serious neuropsychiatric symptoms in patients taking varenicline with recommended dose (*79*). The dose is usually started at a dose of 0.5 mg once daily for the first 3 days, 0.5 mg twice daily for the next four days and then 1 mg twice daily. The half-life of this drug is approximately 17 (± 3) h after repeated dose, with $T_{max}$ 4.3 (± 2.3) h and $C_{max}$ 4.0 (± 0.7) ng/mL (*80*). Recommended duration of treatment is 12 weeks but in special groups of patients, who have had relapse with shorter duration of treatment, varenicline can be taken even for 24 weeks (*4*). No pulmonary delivery of this drug or PK of inhaled varenicline has been investigated so far. Despite some objections with reference to its use, varenicline is perceived by many clinicians and researchers as the effective smoking cessation aid. Like NRT and bupropion, lung drug delivery with better formulations of varenicline may be introduced for a better therapeutic outcome and effectiveness in the management of nicotine addiction. It is expected that the deep lung delivery of this drug would improve the PK/PD profiles for smoking cessation compared to those of existing delivery methods.

The overall justification for the currently available pharmacotherapies for nicotine addiction is to mimic or replace the effects of nicotine by providing an agonist itself or to control the neurobiological mechanisms by NRT. However, these approaches do not show long lasting outcome. It has been reported that under an ideal circumstances the maximum abstinence rates are only 25 to 35% and approximately 80% of patients who used one of the currently available medications returned to smoking within the first year (*81*). Given the evidence, it is now comprehensible that there is a need to develop more effective therapy compared to those of currently available products for long lasting and effective cessation of tobacco smoking. The pulmonary route seems to be ideal for rapid delivery of nicotine in case of NRT or other medications to the brain, where it has its appropriate therapeutic effects. This route would allow quitters to absorb sufficient amounts of nicotine to diminish their smoking urges. Therefore, it would be excellent to develop such a product that can produce better PK/PD profiles following administration by inhalation.

## 6. Summary

Tobacco smoking is strongly associated with an increased risk of developing coronary artery disease, chronic obstructive pulmonary disorder, and cancer (*82*). The odds of successful smoking cessation are improved with pharmacotherapy as reviewed above. These therapies are thought to work primarily by replacing nicotine (*e.g.*, NRT) or modestly stimulating or inhibiting nicotine effects in the brain (*e.g.*, varenicline or bupropion), thereby minimizing withdrawal symptoms experienced during smoking cessation. While the role of effective pharmacotherapy is essential for effective management of nicotine addiction, better formulation with innovative drug delivery might advance therapeutic outcome for various disorders associated with tobacco addiction. It is expected that treatment of nicotine addiction will be improved with least side effects using proposed pulmonary drug delivery method in the coming years. However, insufficient data are available to rank-order the effectiveness of the different cessation agents that are currently on market. Selection of an effective active agent should be individually tailored for each patient. Important factors to consider include patient preference, medication compliance issues, previous experience with cessation agents, and patient characteristics, *e.g.*, contraindications, history of depression, and level of smoking. Finally, pharmacotherapy should be accompanied by appropriate behavioral counseling to enhance long-term cessation rates.

## References


1. WHO. Smoking statistics. *http://www.wpro.who.int/media_centre/fact_sheets/fs_20020528.htm*
2. U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
3. Henningfield JE, Fant RV, Buchhalter AR, Stitzer ML. Pharmacotherapy for nicotine dependence. CA Cancer J Clin. 2005; 55:281-299; quiz 322-323,325.
4. Frishman WH. Smoking cessation pharmacotherapy. Ther Adv Cardiovasc Dis. 2009; 3:287-308.
5. Kenny PJ. Emerging therapeutic targets for the treatment of nicotine addiction. Expert Rev Clin Pharmacol. 2009; 2:221-225.
6. Stack NM. Smoking cessation: An overview of treatment options with a focus on varenicline. Pharmacotherapy. 2007; 27:1550-1557.
7. Newman SP, Pavia D, Clarke SW. How should a pressurized beta-adrenergic bronchodilator be inhaled? Eur J Respir Dis. 1981; 62:3-21.
8. Ikeda A, Nishimura K, Koyama H, Tsukino M, Hajiro T, Mishima M, Izumi T. Comparison of the bronchodilator effects of salbutamol delivered *via* a metered-dose inhaler with spacer, a dry-powder inhaler, and a jet nebulizer in patients with chronic obstructive pulmonary disease. Respiration. 1999; 66:119-123.
9. Cohen HA, Cohen Z, Pomeranz AS, Czitron B, Kahan E. Bacterial contamination of spacer devices used by asthmatic children. J Asthma. 2005; 42:169-172.
10. French DL, Edwards DA, Niven RW. The influence of formulation on emission, deaggregation and deposition of dry powders for inhalation. J Aerosol Sci. 1996; 27:769-783.
11. Islam N, Stewart P, Larson I, Hartley P. Lactose surface modification by decantation: Are drug-fine lactose Ratios the key to better dispersion of salmeterol xinafoate from lactose-interactive mixtures? Pharm Res. 2004; 21:492-499.
12. Islam N, Stewart P, Larson I, Hartley P. Effect of carrier size on the dispersion of salmeterol xinafoate from interactive mixtures. J Pharm Sci. 2004; 93:1030-1038.
13. Newman SP, Clarke SW. Therapeutic aerosols 1 – physical and practical considerations. Thorax. 1983; 38:881-886.
14. Gonda I. Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract. Crit Rev Ther Drug Carrier Syst. 1990; 6:273-313.
15. Byron PR. Prediction of drug residence times in regions of the human respiratory tract following aerosol inhalation. J Pharm Sci. 1986; 75:433-438.
16. Hickey AJ, Martonen TB. Behavior of hygroscopic pharmaceutical aerosols and the influence of hydrophobic additives. Pharm Res. 1993; 10:1-7.
17. Suarez S, Hickey AJ. Drug properties affecting aerosol behavior. Respir Care. 2000; 45:652-666.
18. Gonda I. Targeting by deposition. In: Pharmaceutical Inhalation Aerosol Therapy (Hickey AJ, ed.). Marcel Dekker, Inc., New York, 1992; pp. 61-82.
19. Brain JD, Blancard JD. Mechanisms of particle deposition and clearance. In: Aerosols in Medicine, Principles, Diagnosis and Therapy (Moren F, Dolovich MB, Newhouse MT, Newman SP, eds.). 2nd ed., Elsevier Science Publishers, Amsterdam, 1993; pp. 117-155.
20. Bhavna, Ahmad FJ, Mittal G, Jain GK, Malhotra G, Khar RK, Bhatnagar A. Nano-salbutamol dry powder inhalation: A new approach for treating broncho-constrictive conditions. Eur J Pharm Biopharm. 2009; 71:282-291.
21. Plumley C, Gorman EM, El-Gendy N, Bybee CR, Munson EJ, Berkland C. Nifedipine nanoparticle agglomeration as a dry powder aerosol formulation strategy. Int J Pharm. 2009; 369:136-143.
22. Cheow WS, Hadinoto K. Preparations of dry-powder therapeutic nanoparticle aerosols for inhaled drug delivery. Earozoru Kenkyu. 2010; 25:155-165.
23. Kalantarian P, Najafabadi AR, Haririan I, Vatanara A, Yamini Y, Darabi M, Gilani K. Preparation of 5-fluorouracil nanoparticles by supercritical antisolvents for pulmonary delivery. Int J Nanomed. 2010; 5:763-770.
24. Zhang Y, Zhu J, Tang Y, Chen X, Yang Y. The preparation and application of pulmonary surfactant nanoparticles as absorption enhancers in insulin dry powder delivery. Drug Dev Ind Pharm. 2009; 35:1059-1065.
25. Huang M, Ma Z, Khor E, Lim LY. Uptake of FITC-chitosan nanoparticles by A549 Cells. Pharm Res. 2002; 19:1488-1494.
26. Chono S, Tanino T, Seki T, Morimoto K. Influence of particle size on drug delivery to rat alveolar macrophages following pulmonary administration of ciprofloxacin incorporated into liposomes. J Drug Target. 2006; 14:557-566.
27. Chan TL, Yu CP. Charge effects on particle deposition in the human tracheobronchial tree. Ann Occup Hyg. 1982; 26:65-75.
28. Cass LM, Brown J, Pickford M, Fayinka S, Newman SP, Johansson CJ, Bye A. Pharmacoscintigraphic evaluation of lung deposition of inhaled zanamivir in healthy volunteers. Clin Pharmacokinet. 1999; 36(Suppl 1):21-31.
29. Kuhn RJ. Pharmaceutical considerations in aerosol drug delivery. Pharmacotherapy. 2002; 22(3 Pt 2):80S-85S.
30. Bosquillon C, Préat V, Vanbever R. Pulmonary delivery of growth hormone using dry powders and visualization of its local fate in rats. J Control Release. 2004; 96:233-244.
31. Geller DE, Konstan MW, Smith J, Noonberg SB, Conrad C. Novel tobramycin inhalation powder in cystic fibrosis subjects: Pharmacokinetics and safety. Pediatr Pulmonol. 2007; 42:307-313.
32. Hickey AJ, Lu D, Ashley ED, Stout J. Inhaled azithromycin therapy. J Aerosol Med. 2006; 19:54-60.
33. Stoessl J. Potential therapeutic targets for Parkinson's disease. Expert Opin Ther Targets. 2008; 12:425-436.
34. Xu CX, Jere D, Jin H, Chang SH, Chung YS, Shin JY, Kim JE, Park SJ, Lee YH, Chae CH, Lee KH, Beck GR Jr, Cho CS, Cho MH. Poly(ester amine)-mediated, aerosol-delivered Akt1 small interfering RNA suppresses lung tumorigenesis. Am J Respir Crit Care Med. 2008; 178:60-73.
35. Li HY, Seville PC, Williamson IJ, Birchall JC. The use of amino acids to enhance the aerosolisation of spray-dried powders for pulmonary gene therapy. J Gene Med. 2005; 7:343-353.
36. Garcia-Contreras L, Wong YL, Muttil P, Padilla D, Sadoff J, Derousse J, Germishuizen WA, Goonesekera S, Elbert K, Bloom BR, Miller R, Fourie PB, Hickey A, Edwards D. Immunization by a bacterial aerosol. Proc Natl Acad Sci U S A. 2008; 105:4656-4660.

37. Wee JL, Scheerlinck JP, Snibson KJ, Edwards S, Pearse M, Quinn C, Sutton P. Pulmonary delivery of ISCOMATRIX influenza vaccine induces both systemic and mucosal immunity with antigen dose sparing. Mucosal Immunol. 2008; 1:489-496.
38. Sievers RE. Dry powder aerosol vaccine and antibiotics delivery development to reduce risks of deaths in developing countries. 238th ACS National Meeting, Washington, DC, United States, August 16-20, 2009; PRES-008.
39. Anon. Method of and apparatus for effecting delivery of fine powders. IP.com Journal. 2008; 8:13.
40. Sen H, Jayanthi S, Sinha R, Sharma R, Muttil P. Inhalable biodegradable microparticles for target-specific drug delivery in tuberculosis and a process thereof. US patent 2003-685567 2005084455. 2005 20031016.
41. Rawat A, Majumder QH, Ahsan F. Inhalable large porous microspheres of low molecular weight heparin: *In vitro* and *in vivo* evaluation. J Control Release. 2008; 128:224-232.
42. Cheatham WW, Leone-Bay A, Grant M, Fog PB, Diamond DC. Pulmonary delivery of inhibitors of phosphodiesterase type 5. WO patent 2005-US30028 2006023944. 2006 20050823.
43. Farr SJ, Otulana BA. Pulmonary delivery of opioids as pain therapeutics. Adv Drug Deliv Rev. 2006; 58:1076-1088.
44. Fleischer W, Reimer K, Leyendecker P. Opioids for the treatment of the chronic obstructive pulmonary disease. EP patent 2004-13468 1604666. 2005 20040608.
45. Kleinstreuer C, Zhang Z, Donohue JF. Targeted drug-aerosol delivery in the human respiratory system. Ann Rev Biomed Eng. 2008; 10:195-220.
46. Ali R, Jain GK, Iqbal Z, Talegaonkar S, Pandit P, Sule S, Malhotra G, Khar RK, Bhatnagar A, Ahmad FJ. Development and clinical trial of nano-atropine sulfate dry powder inhaler as a novel organophosphorous poisoning antidote. Nanomedicine. 2009; 5:55-63.
47. Timothy W, Giles MF, Jonathan MM. Pulmonary inhalation of levodopa containing compositions in the treatment of Parkinson's disease and other central nervous system disorders. GB patent 2007-21856 2454480. 2009 20071107.
48. Onischuk AA, Tolstikova TG, Sorokina IV, Zhukova NA, Baklanov AM, Karasev VV, Borovkova OV, Dultseva GG, Boldyrev VV, Fomin VM. Analgesic effect from ibuprofen nanoparticles inhaled by male mice. J Aerosol Med Pulm Drug Deliv. 2009; 22:245-253.
49. Shahiwala A, Misra A. Pulmonary absorption of liposomal levonorgestrel. AAPS PharmSciTech. 2004; 5:E13
50. Graham AN, Johnson ES, Persaud NP, Turner P, Wilkinson M. The systemic availability of ergotamine tartrate given by three different routes of administration to healthy volunteers. Progress in Migraine Research. 1984; 2:283-292.
51. Bartus RT, Emerich DF. Pulmonary delivery in treating disorders of the central nervous system. WO patent 2001-US29311 2002024158. 2002 20010919.
52. Bartus RT, Emerich D, Snodgrass-Belt P, Fu K, Salzberg-Brenhouse H, Lafreniere D, Novak L, Lo ES, Cooper T, Basile AS. A pulmonary formulation of L-dopa enhances its effectiveness in a rat model of Parkinson's disease. J Pharmacol Exp Ther. 2004; 310:828-835.
53. Armer TA, Shrewsbury SB, Newman SP, Pitcairn G, Ramadan N. Aerosol delivery of ergotamine tartrate *via* a breath-synchronized plume-control inhaler in humans. Curr Med Res Opin. 2007; 23:3177-3187.
54. Davison S, Thipphawong J, Blanchard J, Liu K, Morishige R, Gonda I, Okikawa J, Adams J, Evans A, Otulana B, Davis S. Pharmacokinetics and acute safety of inhaled testosterone in postmenopausal women. J Clin Pharmacol. 2005; 45:177-184.
55. Wolff RK. Safety of inhaled proteins for therapeutic use. J Aerosol Med. 1998; 11:197-219.
56. Henningfield JE. Nicotine medications for smoking cessation. N Engl J Med. 1995; 333:1196-1203.
57. Benowitz NL. Neurobiology of nicotine addiction: Implications for smoking cessation treatment. Am J Med. 2008; 121(4 Suppl 1):S3-S10.
58. Benowitz NL, Jacob P 3rd. Nicotine and cotinine elimination pharmacokinetics in smokers and nonsmokers. Pharmacol Ther. 1993; 53:316-323.
59. Benowitz NL, Jacob P 3rd, Denaro C, Jenkins R. Stable isotope studies of nicotine kinetics and bioavailability. Clin Pharmacol Ther. 1991; 49:270-277.
60. Fant RV, Henningfield JE, Shiffman S, Strahs KR, Reitberg DP. A pharmacokinetic crossover study to compare the absorption characteristics of three transdermal nicotine patches. Pharmacol Biochem Behav. 2000; 67:479-482.
61. Molander L, Lunell E. Pharmacokinetic investigation of a nicotine sublingual tablet. Eur J Clin Pharmacol. 2001; 56:813-819.
62. Dempsey D, Tutka P, Jacob P 3rd, Allen F, Schoedel K, Tyndale RF, Benowitz NL. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. Clin Pharmacol Ther. 2004; 76:64-72.
63. Sutherland G, Russell MA, Stapleton J, Feyerabend C, Ferno O. Nasal nicotine spray: A rapid nicotine delivery system. Psychopharmacology (Berl). 1992; 108:512-518.
64. Shiffman S, Fant RV, Buchhalter AR, Gitchell JG, Henningfield JE. Nicotine delivery systems. Expert Opin Drug Deliv. 2005; 2:563-577.
65. Bergström M, Nordberg A, Lunell E, Antoni G, Långström B. Regional deposition of inhaled $^{11}$C-nicotine vapor in the human airway as visualized by positron emission tomography. Clin Pharmacol Ther. 1995; 57:309-317.
66. Henningfield JE, Shiffman S, Ferguson SG, Gritz ER. Tobacco dependence and withdrawal: Science base, challenges and opportunities for pharmacotherapy. Pharmacol Ther. 2009; 123:1-16.
67. Rose JE, Behm F, Turner J. Dry powder delivery system. US patent 95-477562 5687746. 1997 19950607.
68. Andrus PG, Rhem R, Rosenfeld J, Dolovich MB. Nicotine microaerosol inhaler. Can Respir J. 1999; 6:509-512.
69. Sumner W 2nd. Estimating the health consequences of replacing cigarettes with nicotine inhalers. Tob Control. 2003; 12:124-132.
70. Davies JH. Nicotine inhalation therapies – smoking cessation and other medical uses. WO patent 2007-GB2074 2007141520. 2007 20070606.
71. Caldwell B, Dickson S, Burgess C, Siebers R, Mala S, Parkes A, Crane J. A pilot study of nicotine delivery to smokers from a metered-dose inhaler. Nicotine Tob Res. 2009; 11:342-347.
72. Gonda I. Nicotine pulmonary formulation for tobacco use cessation. US patent 2007-931867 2008138398. 2008 20071031.
73. Gonda I, Bruinenberg P, Mudhumba S, Cipolla DC. Smoking cessation approach *via* deep lung delivery of clean nicotine. Respiratory Drug Delivery Europe 2009,

Vol 1, pp. 57-62.
74. Ferry LH. Non-nicotine pharmacotherapy for smoking cessation. Prim Care. 1999; 26:653-669.
75. Lerman C, Niaura R, Collins BN, Wileyto P, Audrain-McGovern J, Pinto A, Hawk L, Epstein LH. Effect of bupropion on depression symptoms in a smoking cessation clinical trial. Psychol Addict Behav. 2004; 18:362-366.
76. Jefferson JW, Pradko JF, Muir KT. Bupropion for major depressive disorder: pharmacokinetic and formulation considerations. Clin Ther. 2005; 27:1685-1695.
77. Tutka P, Zatoński W. Cytisine for the treatment of nicotine addiction: From a molecule to therapeutic efficacy. Pharmacol Rep. 2006; 58:777-798.
78. Coe JW, Brooks PR, Vetelino MG, *et al*. Varenicline: An alpha4beta2 nicotinic receptor partial agonist for smoking cessation. J Med Chem. 2005; 48:3474-3477.
79. Kuehn BM. Studies linking smoking-cessation drug with suicide risk spark concerns. JAMA. 2009; 301:1007-1008.
80. Obach RS, Reed-Hagen AE, Krueger SS, Obach BJ, O'Connell TN, Zandi KS, Miller S, Coe JW. Metabolism and disposition of varenicline, a selective alpha4beta2 acetylcholine receptor partial agonist, *in vivo* and *in vitro*. Drug Metab Dispos. 2006; 34:121-130.
81. Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: Varenicline. Int J Clin Prac. 2006; 60:571-576.
82. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer, a meta-analysis. JAMA. 2008; 300:2765-2778.
83. Lechuga-Ballesteros D, Kuo M-C, Song Y, Bueche B. Aerosol formulation comprising nicotine salts obtained by nicotine base reacted with organic acids. WO patent 2005-US22703 2006004646. 2006 20050628.
84. Pavkov RM, Armer TA, Mohsen NM. Aerosol formulations for delivery of dihydroergotamine to the systemic circulation *via* pulmonary inhalation. WO patent 2004-US29632 2005025506. 2005 20040910.
85. Bennett DB, Tyson E, Mah S, de Groot JS, Hegde SG, Terao S, Teitelbaum Z. Sustained delivery of detirelix after pulmonary administration of liposomal formulations. J Control Release. 1994; 32:27-35.
86. Zheng Y, Marsh KC, Bertz RJ, El-Shourbagy T, Adjei AL. Pulmonary delivery of a dopamine D-1 agonist, ABT-431, in dogs and humans. Int J Pharm. 1999; 191:131-140.
87. Okumu FW, Lee RY, Blanchard JD, Queirolo A, Woods CM, Lloyd PM, Okikawa J, Gonda I, Farr SJ, Rubsamen R, Adjei AL, Bertz RJ. Evaluation of the AERx pulmonary delivery system for systemic delivery of a poorly soluble selective D-1 agonist, ABT-431. Pharm Res. 2002; 19:1009-1012.
88. Jackson B, Bennett DJ, Bartus RT, Emerich DF. Pulmonary delivery for levodopa. WO patent 2003-US8659 2003079992. 2003 20030319.
89. Adjei AL, Zheng J, Gupta PK, Marsh KC, Wu V, Lee DY. Formulations for pulmonary delivery of dopamine agonists. US patent 97-822631 6193954. 2001 19970321.
90. Lunell E, Molander L, Ekberg K, Wahren J. Site of nicotine absorption from a vapor inhaler – comparison with cigarette smoking. Eur J Clin Pharmacol. 2000; 55:737-741.
91. Schneider NG, Olmstead RE, Franzon MA, Lunell E. The nicotine inhaler: Clinical pharmacokinetics and comparison with other nicotine treatments. Clin Pharmacokinet. 2001; 40:661-684.
92. Benowitz NL, Porchet H, Sheiner L, Jacob P 3rd. Nicotine absorption and cardiovascular effects with smokeless tobacco use: Comparison with cigarettes and nicotine gum. Clin Pharmacol Ther. 1988; 44:23-28.
93. Choi JH, Dresler CM, Norton MR, Strahs KR. Pharmacokinetics of a nicotine polacrilex lozenge. Nicotine Tob Res. 2003; 5:635-644.
94. Dalby RN, Hickey AJ, Tiano SL. Medical devices for the delivery of therapeutic aerosols to the lungs. In: Inhalation Aerosols. 2nd ed., Informa Health Care, London, UK, 2006; pp. 417-444.

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