Review

Inhaled nicotine replacement therapy

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ABSTRACT
There are a large number of smokers who want to quit smoking but have failed in their attempts to do so, with many having been unsuccessful at quitting multiple times over their lifetime. The existing marketed nicotine replacement therapies (NRT) have only marginal effectiveness and none provide a comparable physiological response to that derived from cigarette smoking; that is, rapid absorption of nicotine from the lung leading to peak levels of nicotine in the bloodstream to target the receptors in the brain. Instead, existing NRTs produce a slower and delayed rise in nicotine blood levels which is less effective at reducing the craving sensations. Published data for electronic cigarettes show that they typically deliver nicotine with a profile closer to that for nicotine patches, with a slow rise that can take 30–60 min, or longer, to reach the same peak nicotine concentration that is produced in less than 3 min from a single cigarette. A number of attempts have been made to develop an inhaled product which would deliver the nicotine through the lung and mimic the physiological response from smoking, but many of them produced intolerable aversive reactions or delivered an ineffective dose. This paper discusses examples of the potential for the recent inhaled nicotine products in development to be effective as NRTs, but is not meant to be a comprehensive review.

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1. Introduction
Cigarette smoking is harmful, often leading to early mortality, and represents a huge public health problem. At present, cigarette smoking causes more than 480,000 deaths annually in the US, accounting for about one in five deaths, with an estimated 41,000 of these deaths resulting from secondhand smoke [1]. Smoking is the leading cause of death in the US among the preventable risk factors, which include smoking, unhealthy diet, physical inactivity and sexual behavior; smoking kills more people than AIDS, alcohol, illegal drug abuse, homicides, car accidents, and suicide combined (Fig. 1). The issue is even more acute in Asia. Over 300 million smokers reside in China representing more than a third of the smokers worldwide [3]. Men account for 96% of the smokers in China with 52.9% of men and 2.4% of women identified as smokers [3]. One million deaths in China are attributable to cigarettes yearly and this is projected to increase three-fold by 2050 if smoking rates do not change [3]. Worldwide, tobacco use causes nearly 6 million deaths/y. Current trends show that tobacco will cause more than 8 million deaths annually on a worldwide basis by 2030 [4].

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In the US, smoking causes about 90% of all lung cancer deaths in men, and about 80% of all lung cancer deaths in women [5]. However, the ill effects from smoking are not limited to the lung. Cigarette smoking can cause cancer almost anywhere in the body, including the bladder, bone, blood, cervix, esophagus, kidney, larynx, mouth, nose, throat, pancreas, stomach, and trachea. If nobody smoked, it is estimated that one of every three cancer deaths in the US would not happen [5].

Smokers are addicted to nicotine and have great difficulty quitting smoking. However, it must be emphasized that the harmful effects of tobacco smoking are largely due to the other ingredients of tobacco smoke – tar constituents and carbon monoxide – and not nicotine. Fortunately, many of the effects of smoking can be reversed or attenuated after quitting and can add years to the average smoker’s life expectancy [6,7]. Therefore, effective smoking cessation treatment would be enormously beneficial for individuals as well as a public health measure.

For people trying to quit smoking, nicotine replacement therapies (NRTs) on the market today are not very effective at satisfying the craving for cigarettes [8,9]. Thus, NRTs (e.g., patches, lozenges, gums, nasal sprays, and the buccal inhaler) exhibit very modest long term quitting efficacy, generally <10%. In a study of 787 adult smokers in Massachusetts who had recently quit smoking and were evaluated over a 5 y period, the authors concluded that using NRTs is no more effective than trying to quit without the use of NRTs [8]. While clinical studies have found NRTs to be effective versus placebo, this study provides empirical evidence regarding the lack of effectiveness when NRTs are used in the general population [8].

The limited benefit of NRTs is primarily associated with the relatively slow absorption of nicotine into the bloodstream, and ultimately its slow uptake into the brain. Thus, existing NRTs are not an effective substitute for cigarettes as they cannot activate the neural reward pathways in the same way that cigarettes do [9]. Rapid nicotine absorption with a high $C_{\text{max}}$ produces a better reduction in craving and may inhibit relapse [9,10]. Other contributors to relapse may be the absence of the airway sensation experience for NRTs that occurs during tobacco smoking, as well environmental cues that can trigger an urge to smoke; e.g., seeing others smoke or the smell of a cigarette [9].

Among the NRTs, nicotine nasal sprays have the fastest entry of nicotine into the bloodstream (Fig. 2); however, the pharmacokinetics is still not as rapid as that for cigarettes [12]. Furthermore, nicotine nasal sprays deliver relatively high doses of nicotine to a small surface area within the nasal cavity, which can lead to irritation and ultimately lack of acceptability. A nicotine replacement system which delivers nicotine via the inhalation route to the lung therefore has the potential to better satisfy craving and improve quitting rates [9]. While no pharmaceutically-based inhaled NRT system for delivery of nicotine to the lung is on the market, a number are in development [10,13,14] and these will be the focus of the review. For the purposes of this article, pharmaceutically-based NRT systems are defined as those which are manufactured in...
accordance with good manufacturing processes (GMPs) and approved by regulatory agencies based on clinical data.

In contrast, a variety of electronic nicotine delivery devices such as e-cigarettes are already available in many countries which provide an alternative to cigarettes and a potentially ‘safer’ way to inhale nicotine. These devices are promoted specifically without clinical data demonstrating that they reduce cigarette dependence and, as such, they cannot be marketed as NRTs (at least in the US) but instead as tobacco products [15]. E-cigarettes are gaining in popularity and may offer some safety benefits over cigarettes in terms of harm reduction due to elimination of exposure to carcinogenic tobacco combustion products [16]. However, much is unknown about the long-term safety of e-cigarette use as well as the safety of “secondhand” exposure from e-cigarettes. For these reasons and others, e-cigarettes are banned in many countries and restricted in public places in others.

E-cigarettes contain organic solvents and many have chemicals as flavorings, with no proven safety data [17]. Two additional concerns are the potential for the nicotine to decompose due to instability in the e-cigarette formulation and the potential for unintended poisoning from the concentrated liquid nicotine in e-cigarettes [18]. On that note, the Center for Disease Control (CDC) reported that the proportion of nicotine exposure calls to poison control centers due to e-cigarettes surged from 0.3% (1 call) in September 2010 to 42% (215 calls) in February 2014 and furthermore that e-cigarette exposure calls were more likely to report an adverse event than those for cigarettes [18]. There is also much concern about the use of e-cigarettes in nicotine-naïve subjects, especially school children. However, this usage has surfaced only recently, and the initial rise of e-cigarette popularity was ostensibly driven by people who want to quit smoking or reduce cigarette usage [19]. Unfortunately, there is little evidence that e-cigarettes aid in either smoking cessation or a reduction in cigarette consumption [19,20]. Even the “efficacy” of e-cigarettes has been questioned because of the widely variable dosimetry across the over 250 brands on the market [16,17]; e-cigarettes generally produce relatively modest peak levels of nicotine compared to those obtained from cigarettes [9,17].

In contrast, pure nicotine is recognized as safe and non-carcinogenic and is an approved drug for the chronic treatment for smoking cessation in the US and EU as well as many other countries. While tobacco smoke contains ~4000 chemicals, of which ~250 are harmful, and ~50 are carcinogenic, nicotine itself is not a direct carcinogen [1,21]. Nicotine may contribute to some smoking related diseases, but its contribution is generally considered much smaller than the tobacco combustion products, and NRTs do not increase the risk of cancer [22]. Notably, nicotine is contra-indicated in pregnant women because it may cause premature birth and in youths as it affects the developing brain [17]. However, for most smokers addicted to nicotine, an inhaler delivering pure nicotine to the lungs may be preferred and more effective than either e-cigarettes or current NRTs to aid in smoking cessation. A nicotine inhalation product that is economical, simple to use and tailored to the needs of smokers [23], which delivers a consistent dose of nicotine to the deep lung in one or two puffs, has the potential to address the limitations of current NRTs. The opportunity for inhaled NRTs is discussed in this review.

2. Requirements for an effective nicotine inhaler

The large number of smokers who are unable to quit represents a significant market opportunity for an effective smoking cessation product, not only in terms of product sales but also with respect to the positive healthcare benefit to individuals and society at large. A properly-designed inhaler providing nicotine pharmacokinetics similar to that for cigarettes has the potential to address a number of the acceptability issues with the currently marketed NRTs [24]. Previous attempts with ‘nicotine inhalers’ including metered dose inhalers failed due to upper airway irritation, poor deep lung delivery, and formulation problems [9]. So it is critical that the performance of the inhaler be designed to minimize delivery of nicotine aerosol to the oropharynx and upper airways, and ensure that a reproducible and effective dose reaches the deep lung. This can be achieved by proper control of the primary parameters which affect deposition in the oropharynx and lung, the inhalation flow rate and aerosol particle size distribution. Other factors are also important including the timing and length of the aerosol generation process, proper coordination of the inhalation maneuver with onset of aerosol delivery and the potential for particle growth or evaporation during transit.

Deposition of a significant fraction of the nicotine aerosol in the oral cavity will provoke cough leading to poor product acceptability [9]. In addition, coughing interrupts the inspiration maneuver and so results in low or inconsistent delivery of the nicotine aerosol to the deep lung. High oropharyngeal deposition and its inherent aversive response is what torpedoed the early attempts to use nicotine metered dose inhalers (MDIs) [9]. Particle deposition in the oropharynx is primarily due to inertial impaction which increases with both particle size and inhalation flow rate; together these two factors impart greater momentum to particles [25]. Thus, a properly designed nicotine inhaler can overcome this challenge by producing aerosols with predominantly small droplets, typically with aerodynamic diameters less than ~5 μm, inhaled at relatively slow flow rates; e.g., <30 l/min [25].

An additional requirement is to deliver a consistent and effective dose of nicotine to the deep lung where it can rapidly be absorbed into the bloodstream, which drives delivery of high peak nicotine concentrations to the brain. An outcome of avoiding significant deposition of nicotine in the oral cavity is that the majority of the generated aerosol has the potential to deposit in the deep lung; however, very small particles may be exhaled (and that is the primary reason that secondhand exposure to cigarette smoke is such a concern) [25]. To circumvent exhalation of particles, the aerosol particles should be greater than ~1 μm [25,26]. Thus, an aerosol between around 1 and 5 μm, inhaled at a slow flow rate, is required for deep lung deposition and rapid absorption of nicotine.

Furthermore, the nicotine dose delivered to the lung should be adequate to achieve peak blood levels of nicotine comparable to that for cigarettes; e.g., a mean of 19 ng/ml [27] to 26 ng/ml [28] was reported for venous and 35 ng/ml [29] for arterial blood sampling. If the inhaler does not deliver the nicotine to the deep lung, or is not formulated for rapid absorption, then it will be difficult to achieve these nicotine levels in a comparable
these excipients should be selected with care as they can also lead to slower uptake across the lung and thus lower systemic peak nicotine levels. Furthermore, there is the possibility for overdosing if the aversive sensation is completely eliminated, or if there is a delay in absorption, combined with the consumer inhaling additional doses with the mistaken belief they did not receive an effective dose.

3. Inhaled nicotine replacement therapies in development

3.1. The AERx essence pure nicotine inhaler (Aradigm, Hayward, CA)

The AERx platform of inhalation devices has been tested in thousands of patients under US Investigational New Drug (IND) Applications for a variety of drug and biologics products and no safety issues have been associated with the platform [26]. The key reason for the safety is that the formulations typically consist of a small amount (~50 μl) of an aqueous solution of drug or biologic, free of organic solvents and innocuous chemicals. The specific platform used for delivering nicotine is based on the palm-size prototype called the AERx Essence, which was tested in several clinical trials including one with nicotine [26,33]. The follow-on AERx nicotine inhaler is designed to be about the size of a small smart phone – which has been proven to be the size of arguably the most popular consumer product on a global scale. It does not produce any “second-hand smoke”, in contrast to cigarettes or e-cigarettes. The AERx nicotine inhaler does not require any batteries or external power [26].

The AERx nicotine inhaler consists of a durable purely mechanical device and a single dose disposable dosage form (strip) containing the nicotine formulation (Fig. 4A). The formulation consists of pharmaceutical grade stable nicotine salt solution in pure water as the only other excipient [10,24]. The operation of the device involves simply opening the device, inserting the nicotine strip, closing the device, initiating inspiration and pushing the button to actuate delivery in a single breath [26]. The inhaler synchronizes generation of the aerosol with the initiation of inspiration and it also controls the flow rate during inhalation to ensure that a reproducible dose is delivered [26].

The in vitro performance of the AERx Essence system (4 prototype devices that were used in the clinical trial in smokers described below) was characterized across a range of nicotine concentrations from 5 to 40 mg/ml with a linear response in nicotine delivered dose versus loaded dose ($r^2 = 0.99$) [13]. Strips were filled with a nicotine salt (nicotine bitartrate) dissolved in water at pH 3.0–3.1. The formulations were placed on stability at 25 °C and 40 °C for 9 months, with no formulation changes in pH and no meaningful changes in nicotine concentration or aerosol performance [13]. The 10, 20 and 30 mg/ml nicotine concentrations translate to a device loaded dose of 0.5, 1.0 and 1.5 mg nicotine. The aerosol particle size distribution was relatively insensitive to nicotine concentration with a mass median aerodynamic diameter (MMAD) ranging from ~2.4 to ~2.8 μm for the 10–30 mg/ml nicotine concentrations, respectively, with a
geometric standard deviation (GSD) of 1.3 for both [13]. The amount of emitted aerosol in particles less than 4.95 μm in size, termed the fine particle dose, was 0.23, 0.48 and 0.73 mg, for the 0.5, 1.0 and 1.5 mg loaded dose, respectively [13]. The fine particle dose is a reliable estimate of the dose that deposits in the lung [33]. The highest AERx nicotine dose of 0.73 mg thus represents about 50% of the 1–2 mg lung dose from a typical cigarette. While a cigarette is typically inhaled over seven to ten puffs, for the AERx nicotine inhaler the dose is given in a single inhalation.

The pharmacokinetics (PK) of inhaled nicotine from the AERx Essence device was studied in a phase 1 human clinical trial in 18 participants [10]. The PK profiles for all three nicotine doses from a single inhalation show a maximum arterial blood level at the first time point, 1 min post administration (Fig. 5). The nicotine levels decrease from the peak over time to produce profiles comparable to that for cigarettes (Fig. 5). An increase in the nicotine dose, from 0.23 to 0.73 mg, resulted in an increase both in the peak ($C_{max}$) and extent of absorption (AUC), with a trend toward dose proportionality [13].

The efficacy of the same three dose levels was also evaluated in a subset of subjects ($n = 16$) by monitoring their craving levels on a 10 point visual analog scale (with a score of 0 representing no craving at all and 10 representing most craving ever) prior to administration of the inhaled nicotine and then for the next 4 h [13]. For all three dose levels the initial craving score was between 4 and 6, indicating a moderate desire to smoke (Fig. 6). The craving score immediately decreased by 3–4 units at the first time point (2 min) following dosing and remained low (below 3) for 60 min for all three dose levels (Fig. 6) and remained below pre-baseline craving levels for 4 h, which was the end of the study [13]. Nearly all subjects reported an acute reduction in craving or an absence of craving immediately following study dosing. While the craving was acutely reduced, in line with the appearance of rapid peak systemic nicotine plasma levels, there did not appear to be a dose response across the three nicotine levels (Fig. 6). This result suggests that a lower nicotine dose than in cigarettes may be effective as an NRT.

Regarding safety measures (e.g., vital signs, ECG, spirometry, and labs (full blood count, renal function tests, glucose, liver function tests, alkaline phosphatase, serum electrolytes, and urine macro panel and microscopy)), no clinically significant changes were observed following dosing. Mild and moderate acute adverse events were noted, typically involving cough, throat irritation or light-headedness, similar to the effects of nicotine from cigarette smoking, and these self-resolved without medication. Thus, inhaled nicotine across the 0.23–0.73 mg range using the AERx Essence system appears safe and tolerable with a PK profile that is consistent with the rapid delivery and absorption of nicotine observed with cigarettes.

3.2. Voke® nicotine metered dose inhaler (Kind Consumer Ltd., London, UK)

The Voke System (Fig. 4B) is a nicotine delivery device based on metered dose inhaler (MDI) technology and comprises an MDI reservoir and a ‘stick’ that delivers the nicotine to the subject [13,34–36]. The MDI reservoir contains 20 doses of 0.056% (w/w) nicotine formulated in propylene glycol, ethanol,
saccharin, menthol, and HFA134a propellant. The number of doses is patterned after cigarettes which contain 20 cigarettes per pack. The ‘stick’ is charged with nicotine from the MDI and the subject inhales 6–8 times from the ‘stick’ to receive the complete dose of 0.43 mg nicotine. The stick is triggered to deliver the nicotine aerosol within 0.5 s upon inhalation at a flow rate of at least 2–3 l/min [34,35], comparable to inspiratory flows smokers typically draw when smoking cigarettes. This is in contrast to pharmaceutical MDIs which are typically inhaled at much faster flow rates of 60 l/min [25].

The in vitro performance of the Voke has been characterized with the mean emitted dose falling within 75–125% of the 0.43 mg nicotine nominal dose, even after storage for up to 18 months at 25 °C/60% RH or 30 °C/65% RH [34]. The fraction of the aerosol less than 5 μm, termed the fine particle fraction (FPF), was 80% of the emitted dose, yielding an in vitro fine particle dose (FPD) of 0.29–0.37 mg nicotine per complete dose from the stick.

The pharmacokinetics of the Voke nicotine inhaler has been tested in 18 smokers (who smoke ≥ 10 cigarettes/d with their first cigarette within an hour of waking) in a Phase 1 human clinical trial [13,36]. Three doses were evaluated: 0.22, 0.45 and 0.67 mg nicotine, which were delivered in 6–8 puffs over a 2 min period [13,36]. The mean maximum arterial nicotine concentration for the 0.22, 0.45 and 0.67 mg nicotine doses was 2.11, 3.73, and 4.38 ng/ml, respectively, which was achieved after 10.2, 7.3, and 6.5 min from the start of inhalation for each of the three doses, respectively (Fig. 5) [13]. In contrast to the Nicorette® Inhalator, for which the nicotine is absorbed buccally and results in earlier and higher venous than arterial nicotine levels, the Voke inhaler has earlier and higher arterial nicotine levels than

![Fig. 5 – Mean arterial nicotine levels for the AERx Essence System and the Voke Inhaler. The pharmacokinetic profiles are adapted from References 10 and 13. The sample sizes are n = 5, 6, and 5 for AERx 0.73, 0.48 and 0.23 mg nicotine, respectively [10], and n = 6 for all three Voke groups [13].](image)

![Fig. 6 – Reduction in craving for the AERx Essence System and the Voke Inhaler versus the Nicorette Inhalator. The mean craving scores are adapted from References 10 and 34. The sample sizes are n = 5, 6, and 5 for AERx 0.73, 0.48 and 0.23 mg nicotine [10], respectively, and n = 24 for both Voke groups and the Nicorette Inhalator [34].](image)
venous levels, suggesting more pulmonary nicotine absorption [13]. However, the peak arterial nicotine concentration using the Voke inhaler represents only 5–10% of what is typically achieved from smoking one cigarette, likely due to slower absorption of nicotine from the Voke inhaler compared to that for cigarettes [13].

The participants in the study (n = 24) were also evaluated for the ability of the nicotine dose (0.45 or 0.67 mg) to reduce their craving for smoking compared to the Nicorette Inhalator, which delivers ~4 mg nicotine (Fig. 6) using a visual analog scale with a score of 0 representing no craving and 10 representing strong craving [36]. Craving scores for both doses from the Voke Inhaler showed a drop at the first time point tested, 4 min post administration, which were comparable to the drop for the approved Nicorette Inhalator. The craving scores for the 0.45 mg Voke dose and the Nicorette Inhalator both reached a nadir at the 20 min time point post administration (Fig. 6) and gradually increased back to their pretreatment values over the subsequent 280 min [36]. In spite of the 50% lower overall nicotine exposure from the 0.45 mg Voke inhaler, it was at least as effective as the Nicorette Inhalator in reducing craving scores and superior at some time points post dose (reaching statistical significance at the 180 and 240 min time points) [36].

In both the PK and craving efficacy element of the trial a number of adverse events were reported, mostly related to study medication [13,36]. In the pharmacokinetic substudy there were a total of 56 adverse events in 16 (89%) subjects including oral paresthesia, throat irritation, headache, dizziness, dry throat and cough [13]. Tolerability symptoms were reported in two-thirds of the subjects [13]. In the craving substudy, a total of 87 adverse events were reported in 23 (96%) participants, but all were mild or moderate in nature, similar to those reported in the PK substudy [36].

3.3. The staccato evaporative condensation system (Alexza Pharmaceuticals, CA, USA)

The Staccato® system (Fig. 4C) is a hand-held device which delivers a condensation aerosol following rapid vaporization of the drug from the drug-coated stainless steel substrate element in the device [37]. The device is breath-actuated and delivers aerosol, which is within the respirable size range of 1–5 μm [37]. The device incorporates a valve to control the inhalation rate and thus the rate of drug vaporization [37]. This technology is already approved and marketed for delivery of loxapine for acute treatment of agitation associated with schizophrenia or bipolar I disorder [38]. The Staccato system for delivery of nicotine is at an earlier stage of development and there is no human safety or efficacy data [14]. The deposition of drug in a film layer on the substrate element is typically achieved by solubilizing the drug in a solvent (ethanol, acetone, chloroform, hexane or methanol) and applying it by a spray coating process [37]. For drugs like nicotine which are liquids at ambient temperatures, this process is not used. Instead, nicotine is complexed with a zinc halide (ZnBr₂(nicotine)₂ and ZnCl₂(nicotine)₂) to facilitate spray coating [14]. The Staccato system was able to achieve an emitted dose of nicotine of ~100 μg, comparable to that in a single puff from a cigarette [14]. However, 43% of the emitted nicotine was in a vapor form, and the other 57% in particle form had a mean particle size of 0.8 μm (Volume Mean Diameter), suggesting that much of the dose would be exhaled.

There are no published reports of the performance of this system for delivery of nicotine in animals or humans.

4. Results and discussion

Interest in developing an inhaled NRT that is effective for people wanting to quit smoking has escalated, in line with the growing popularity of e-cigarettes. A number of inhaled nicotine delivery systems were reviewed in this article. The Staccato system containing the drug loxapine for the treatment of psychotic episodes is on the market and provides rapid and reproducible systemic absorption following inhalation with a T_{max} of 2 min [38], suggesting that it may also have the potential to deliver inhaled nicotine rapidly to the bloodstream. However, there is no published inhalation safety data on the nicotine metal complex used in the Staccato formulation, nor whether inhaled nicotine is well-tolerated and rapidly absorbed from this system, which is a requirement of an effective smoking cessation product. The Staccato technology has potential for use as an NRT but more preclinical and clinical data are needed to make an informed evaluation.

A recent review article concludes that “inhalers can deliver nicotine more efficiently than other nicotine products, facilitating smoking cessation and improving smoker’s lives” [9]. Those authors conducted a phase 1 clinical trial with a metered dose inhaler product, different from the Voke inhaler, but found similar PK profiles with a slower T_{max} (5–6 min) than for cigarettes (2 min), indicating that most of the nicotine in the MDI aerosol was absorbed more slowly via the oropharynx and upper airway [28]. This MDI was able to achieve higher peak nicotine concentrations than for the Voke inhaler of 9.4–12.5 ng/ml for the two dose levels (0.5 and 1 mg, respectively), but are still lower than that for the cigarette (25.9 ng/ml) [28]. To achieve these peak nicotine levels, it was necessary to administer twenty inhalations from the MDI spacer over a 5 min period [28]. The bioavailability was 19.5% (0.5 mg) and 35% (1.0 mg) for the MDI compared to the 1.1 mg nicotine content delivered by the cigarette [28]. Even though significant discomfort (e.g., coughing and interruption in inspiratory flow) was reported by the participants, both doses also reported reductions in craving [28]. While the Voke inhaler appears to be in a more portable and pleasing format for smokers, this MDI and spacer were in a traditional pharmaceutical presentation and would likely need to be redesigned for the smoking cessation market.

While there appear to be limitations with both MDI products discussed above, including aversive aerosols, extended administration times, and delayed (and low) peak PK profiles, they support the concept that a nicotine inhaler can provide a reduction in craving for cigarettes. The Voke Inhaler (0.45 mg nicotine) recently received a product license for general sale from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and may reach consumers in 2015 [39]. The license is for the relief and/or prevention of craving and nicotine withdrawal symptoms associated with tobacco dependence. The indication includes smokers wishing to quit or reduce cigarette use prior to quitting, as well as situations where smokers are unable to smoke, and as a safer alternative to
smoking for smokers and those around them. The medical device component of the Voke nicotine inhaler has also received the CE mark that is required for medical devices sold in the European Union. These approvals are necessary given the MHRA’s 2013 decision that all nicotine containing products sold in the UK will require a license by 2016 [40].

In contrast, the craving for a cigarette can be satisfied in a single breath from the AERx nicotine inhaler discreetly, in less than one min. The PK profile from the AERX system reaches a peak at the first blood draw of 1 min post administration, indicating aerosol deposition in the deep lung facilitating rapid absorption, comparable to the deposition and absorption profile from cigarettes [13]. This rapid absorption of nicotine was associated with an immediate drop (2 min post dose) in the craving score [13]. The duration of effect was prolonged, remaining below pretreatment baseline levels for 4 h. Furthermore, all three doses had comparable reductions in craving scores, suggesting the potential for the AERX nicotine inhaler to be needed less often than for cigarettes, and exposing the subject to only a fraction of the nicotine dose in cigarettes.

The AERX nicotine inhaler is purely mechanical, requiring no batteries, no heating of the product, and will offer precise control of delivery with extremely low probability of accidental overdose. Furthermore, the AERX nicotine inhaler will not have the attraction to children that cigarettes and e-cigs do, as it is a discrete product used once every few hours in contrast to the more frequent use of cigarettes and e-cigarettes. The total daily dose of nicotine from the AERX nicotine inhaler will likely be lower than for other NRTs (e.g., patches) and for cigarettes. The delivery of nicotine using the AERX Essence Inhaler may one-day offer a convenient, safe, effective and socially acceptable alternative to smoking by satisfying periodic craving episodes to help those who want to quit smoking [10,24].

5. Conclusion

Given the marginal effectiveness of the current marketed NRTs to facilitate smoking cessation, the market opportunity and societal benefit for an effective inhaled NRT is huge. An inhaled NRT has the potential to provide the same physiological response that smokers receive from cigarettes and so may successfully address the craving episodes and other symptoms of nicotine withdrawal. Among the nicotine inhalers covered in this review, the AERX Essence System is the only nicotine inhaler that has demonstrated the ability to rapidly deliver peak arterial nicotine levels in under a minute that are comparable to those achieved during cigarette smoking. Administration of inhaled nicotine from the AERX Essence System was associated with a rapid and prolonged reduction in craving for cigarettes for at least 2 h. These results suggest that an inhaled nicotine system like the AERX Essence System, once approved as an NRT, could be used by smokers as an aid for smoking cessation.

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