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Source: *Nicotine & Tobacco Research*, October 2012, Vol. 14, No. 10 (October 2012), pp. 1127-1139

Published by: Oxford University Press

Stable URL: <https://www.jstor.org/stable/10.2307/26763585>

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Review

A Systematic Review of Nicotine by Inhalation: Is There a Role for the Inhaled Route?

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Received July 2, 2011; accepted January 11, 2012

Abstract

Introduction: A considerable minority of adults remain addicted to smoking cigarettes despite substantial education and public health efforts. Nicotine replacement therapies have only modest long-term quit rates. The pulmonary route of nicotine delivery has advantages over other routes. However, there are regulatory and technical barriers to the development of pulmonary nicotine delivery devices, and hence, none are commercially available. Current knowledge about pulmonary nicotine delivery is scattered throughout the literature and other sources such as patent applications. This review draws together what is currently known about pulmonary nicotine delivery and identifies potential ways that deep lung delivery can be achieved with a simple portable device.

Aims: To systematically review clinical trials of nicotine inhalers, determine whether they delivered nicotine via the lung, and identify ways that pulmonary delivery of medicinal nicotine might be achieved and the technical issues involved.

Methods: Systematic search of Medline and Embase.

Results: Thirty-eight trials met the inclusion criteria. Cough, reflex interruption of smooth inspiration, and throat scratch limited the usefulness of nicotine inhalers. The pharmacokinetic profiles of portable nicotine inhalers were inferior to smoking, but among commercially available products, electronic cigarettes are currently the most promising.

Conclusions: Pulmonary nicotine delivery might be maximized by use of nicotine salts, which have a more physiological pH than pure nicotine, by ensuring the mass of the particles is optimal for alveolar absorption, and by adding flavoring agents. Metered-dose inhalers potentially can deliver nicotine more efficiently than other nicotine products, facilitating smoking cessation and improving smokers' lives.

Introduction

There is growing interest in nontobacco nicotine inhalation, both as a recreational alternative to smoking and as a therapeutic

tool for smoking cessation. To our knowledge, no reviews have been published that specifically examine nicotine inhalation devices. In light of this, we have systematically reviewed clinical trials of nicotine inhalation devices to identify technical insights that might lead to more effective therapeutic nicotine inhalers.

The Limitations of Current Nicotine Replacement Therapy

Nicotine replacement therapy (NRT) doubles smokers' chances of quitting, compared with placebo therapy (Silagy, Lancaster, Stead, Mant, & Fowler, 2004; Stead, Perera, Bullen, Mant, & Lancaster, 2008), in spite of a number of shortcomings, including the following:

1. Long-term quit rates are low. Only 10% of smokers who try to quit remain abstinent after 12 months (Balfour, Benowitz, Fagerström, Kunze, & Keil, 2000; Institute of Medicine, 2001). Active NRTs only increase quit rates by 7% over placebo 4 years after a single treatment (Etter & Stapleton, 2006);
2. NRTs may have side effects that limit their use, such as local irritation, nausea/vomiting, coughing, hiccup, dyspepsia, and sleep disturbances (Caldwell, Burgess, & Crane, 2010; Wu, Wilson, Dimoulas, & Mills, 2006); the limited variety of delivery mechanisms and dosages restricts people's ability to tailor their nicotine dose in a manner that minimizes side effects and increases efficacy (Cummings & Hyland, 2005);
3. Current NRTs are not very rewarding. Therefore, smokers rarely use them regularly enough to quit smoking (Cummings & Hyland, 2005; Shiffman, Hughes, Pillitteri, & Burton, 2003) and may not spontaneously use NRT in response to smoking cues such as celebrating or coping with boredom;
4. NRT does not control urges to smoke in response to conditioned cues, such as advertising (Henningfield, 1987);
5. NRTs cannot always be used in the situations in which smokers feel the strongest urges to smoke (Hatsukami, Morgan, Pickens, & Champagne, 1990), for instance, drinking alcohol or coffee interferes with absorption of nicotine from oral NRT products;
6. NRT administration routes are embarrassing or unappealing to some smokers (Schneider et al., 2006); and

doi:10.1093/ntr/nts009

Advance Access Published on February 29, 2012

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7. NRT does not fully suppress weight gain after cessation of smoking (Hughes, 1993; Parsons, Shraim, Inglis, Aveyard, & Hajek, 2009). NRT is less effective than smoking for self-medication of various health problems.

As a result of these shortcomings, only 38% of smokers have ever used NRT (Bansal, Cummings, Hyland, & Giovino, 2004) and less than 20% choose to use NRT as part of their quit attempts (Cummings & Hyland, 2005). Even if the proportion of quit attempts that are assisted by current forms of NRT increased to 100% between 2005 and 2025, only 0.5% of smoking-related deaths would be avoided (Apelberg, Onicescu, Avila-Tang, & Samet, 2010). A much greater reduction in smoking would be achieved if more effective NRTs became available (Levy, Mabry, Graham, Orleans, & Abrams, 2010). The development of pulmonary nicotine devices may help to achieve this.

The Advantages of Inhaled Nicotine

NRTs might be more effective if they matched cigarette smoking's nicotine pharmacokinetics, rewarding effects, and psychosocial roles (Hughes, 2001). As with many rewarding drugs, nicotine delivery speed correlates with reinforcement (Benowitz, 1993a, 2008; de Wit, Bodker, & Ambre, 1992; Henningfield & Keenan, 1993; Volkow, Fowler, & Wang, 2002). Depending on the way they are smoked, cigarettes deliver high arterial doses of nicotine to the brain of 34.5 ng/ml on average (Armitage et al., 1975), with a mean nicotine boost in venous blood at 1 min of 11.24 ng/ml in one study (Herning, Jones, Benowitz, & Mines, 1983) and 21.8 ng/ml in another (Henningfield, London, & Benowitz, 1990). Smoking pairs rapid, addictive nicotine delivery (Rose, Mukhin, et al., 2010) with respiratory sensory stimulation (Rose, Behm, Westman, Bates, & Salley, 2003). Nicotine causes the release of rewarding neurotransmitters when it binds to cerebral nicotinic acetylcholine receptors (nAChR). Nicotine exposure may desensitize nAChR for hours, but a Pavlovian response to conditioned stimuli, such as respiratory sensory experiences, provides a second reward pathway (Balfour, 2004; Rose et al., 2003). However, because currently available NRTs do not rapidly deliver nicotine via the lung, they cannot activate rewarding neural pathways in quite the same way as smoking does, which limits their capacity to act as substitutes for smoking.

The pulmonary route is the fastest practical way to deliver nicotine to the brain (Dar & Frenk, 2007; Gonda, 2006; Leach, 2007; Russell & Feyerabend, 1978). A pulmonary NRT would deliver rapid boli of nicotine to "peak seekers" and allow "trough maintainers" to titrate their nicotine intake precisely to suit their nicotine metabolism and their nAChR sensitivity (Balfour, 2004; Glautier, 2004; Russell, 1988; Watkins, Koob, & Markou, 2000).

Rapid pulmonary delivery of nicotine also reinforces use via transient increases in heart rate and blood pressure, similar to other drugs of addiction (Henningfield, Stapleton, Benowitz, Grayson, & London, 1993). Acute cardiovascular effects are more pronounced when a high dose of nicotine is delivered rapidly, via the lung, compared with slower oral or transdermal administration (Benowitz, Gourlay, Benowitz, & Gourlay, 1997). These physiological and sensory effects heighten arousal and enhance the pleasure of associated activities, such as drinking alcohol or coffee, celebrating, relaxing, or socializing (Best & Hakstian, 1978; Dunbar, Scharf, Kirchner, & Shiffman, 2010;

Rose & Behm, 1991). Inhalation of nicotine is more suited than oral or transdermal nicotine to many social smoking contexts. Pulmonary delivery of nicotine in these contexts ensures that they remain as enjoyable as they were when smoking (Balfour, 2004). Pulmonary delivery of nicotine is also well suited to situations in which smokers wish to reduce their anxiety, impulsivity, and boredom (Pettiford et al., 2007; West, 1992) or to obtain one of nicotine's potential medical benefits.

Compared with oral or transdermal delivery, delivery of equal doses of nicotine to pulmonary alveoli results in a larger acute cerebral dose—inhaled nicotine therefore can achieve a high ratio of psychoactive effects to systemic side effects (Cummings & Hyland, 2005; Dar & Frenk, 2007; Russell & Feyerabend, 1978; Russell, Feyerabend, & Cole, 1976). If NRTs were similarly rewarding, smokers might persevere with NRTs despite their side effects.

Many of the therapeutic effects that smokers seek require that nicotine be inhaled. However, there are challenges to overcome in delivering nicotine to the lung. First, the nicotine particles have to be an ideal size and mass. Second, the aversion to inhaling nicotine must be circumvented. These issues are outlined in the discussion.

Therapeutic Applications of More Effective NRTs

The development of new NRTs and improved methods for encouraging smokers to use them may further reduce the prevalence of smoking and its associated morbidity and mortality (Henningfield, Fant, Gitchell, & Shiffman, 2000; McRobbie, Whittaker, & Bullen, 2006; Royal College of Physicians, 2007). Interestingly, although the pulmonary delivery route was first reported in 1967 by Herxheimer, Griffiths, Hamilton, and Wake, it has only recently attracted significant attention. In part, this reflects regulatory authorities' initially cautious approach to all forms of NRT (McNeill, Foulds, & Bates, 2001).

Highly effective NRTs would be useful as long-term nicotine therapy, whether to prevent relapse to smoking or to treat a range of medical conditions (Le Houezec, 1998). Some smokers find it very hard to quit, such as those who are highly nicotine dependent, suffer from mental illness, or are addicted to other drugs. These smokers need palatable, effective, and safe nicotine maintenance therapy (Fagerström, 2002; Gray et al., 2005; Warner, Slade, & Sweanor, 1997). Although it is desirable to replace tobacco smoke as a source of nicotine (Thomson, Wilson, Blakely, & Edwards, 2010), it may not be appropriate, desirable, or even possible to end all nicotine use (Sumner, 2006).

Aim

The aim of this report is to review clinical trials of nicotine inhalation devices, with attention to the technical issues involved in delivery of nicotine to the lung.

Methods

Medline and Embase 1947 to present were searched in February 2011. The search strategy, inclusion criteria, and methods are available as Supplementary material online.

Results

The identification of trials is summarized in Supplementary Figure 1. The articles are organized into groups below according to the type of inhaler. The quality of the included trials was variable (Supplementary Table 1), as were their characteristics (Supplementary Table 2), and the pharmacokinetic profiles of the inhalers that they tested (Supplementary Table 3; all available in the Supplementary material online).

Nebulizers

Lux and Frecker investigated the cardiovascular and subjective effects of inhaling nicotine from a large custom-made nebulizer, which delivered 10 puffs of approximately 100 µg of nicotine per puff over 8 min (Lux & Frecker, 1988a). The pH was titrated to 5.5 by mixing nicotine base with nicotine hydrogen tartrate, the mass median aerodynamic diameter (MMAD) was 0.5 µm, and the concentration of nicotine was 0.45 mg/ml in the nebulizer. This delivered 100 µg of nicotine per 3-s puff. The pharmacokinetics was similar to the reported pharmacokinetics of smoking. This device resulted in statistically significant effects on desire for a cigarette, relaxation, discomfort, and well-being, compared with placebo inhalation or intravenous nicotine (Lux & Frecker, 1988b).

Three reports involved bench-top nebulizers. One found that both nicotine and capsaicin aerosols elicited dose-dependent cough (Hansson, Choudry, Karlsson, & Fuller, 1994). Another observed cough and irritation and a $T_{\max}$ of 2.5 min, with an aqueous solution of nicotine at pH of 10 (Burch, Erbland, Gann, & Hiller, 1989). A similar study of aqueous, large MMAD aerosols reported a $T_{\max}$ of 7.5 min and substantial aversion regardless of variations in their pH; however, the effect of pH was confounded by their very high nicotine concentration and large MMAD (Burch et al., 1993).

Unmetered Inhalers

The Nicotrol/Nicorette/Favor/Pharmacia inhalers (oral inhalers) consist of a plastic tube with a plug of freebase nicotine and menthol at one end, through which the user inhales. They replicate the hand-to-mouth action of smoking and provide upper airway sensory stimulation; however, they produce gas-phase nicotine, which deposits in the oral mucosa rather than the lung. This results in inferior pharmacokinetics and pharmacodynamics, compared with smoking (Lunell, Bergstrom, Antoni, Langstrom, & Nordberg, 1996; Lunell, Molander, Ekberg, & Wahren, 2000; Schneider, Olmstead, Franzon, & Lunell, 2001), and inferior satisfaction, relaxation, and reduction in craving compared with smoking standard or even denicotinized cigarettes (Barrett, 2010). The oral inhaler produced a moderate "good drug effect" but had substantial side effects and was less well liked than smoking (Schuh, Schuh, Henningfield, & Stitzer, 1997). Oral inhaler trial results are mixed. The inhaler had superior short-term quit rates compared with placebo or other treatments, but this was no longer significant 6 months after treatment, even when combined with other treatments (Schneider et al., 1996). Compared with placebo, quit rates with oral inhaler monotherapy were not significantly higher; the combination of oral inhaler plus patch produced higher quit rates but this was not significant beyond 6 weeks, whereas active patch monotherapy had significantly higher quit rates

throughout a 12-month trial (Hand, Edwards, Campbell, & Cannings, 2002; Tonnesen & Mikkelsen, 2000). Other trials found that compared with placebo, the oral inhaler significantly increased long-term quit rates (Hjalmarsen, Nilsson, Sjöström, & Wiklund, 1997; Tonnesen, Norregaard, Mikkelsen, Jorgensen, & Nilsson, 1993) and decreased craving and withdrawal symptoms (Lunell, Molander, Leischow, & Fagerström, 1995). However, this reduction in craving may be related to perceived nicotine content, not actual nicotine content (Darredeau & Barrett, 2010). The oral inhaler was as effective as gum, patch, or nasal spray (Hajek et al., 1999; West et al., 2001), and its abuse potential was intermediate between that of patches and nasal spray (West et al., 2000). Oral inhaler monotherapy had a lower quit rate compared with bupropion monotherapy, but dual therapy with bupropion had a higher quit rate than either oral inhaler or bupropion monotherapy (Croghan et al., 2007, 2010). Twelve-week quit rates were similar with oral inhaler monotherapy, oral inhaler + patch, bupropion, and patch monotherapy (Roth, Andrus, & Westman, 2005). In terms of smoking reduction, the oral inhaler was more effective than placebo treatment (Bolliger et al., 2000; Rennard et al., 2006) but less effective than electrically heated tobacco (Fagerström, Hughes, Rasmussen, & Callas, 2000). Compared with the oral inhaler, other NRTs were more greatly preferred (Fagerström, Tejding, Westin, & Lunell, 1997), or equally preferred (Bolliger, Van Biljon, & Axelsson, 2007), and had similar quit rates (Bolliger et al., 2007) and smoking reduction rates (Fagerström et al., 1997). Subjects used the oral inhaler more often than other NRTs; however, the oral inhaler was considered less suitable as an NRT (Schneider, Cortner, Gould, Koury, & Olmstead, 2008; Schneider et al., 2004, 2006). Compared with placebo, the oral inhaler improved the mood of females but had the opposite effect in males (File, Fluck, & Leahy, 2001). The oral inhaler had no acute effect on airway blood flow or airflow (Randhawa, Mendes, & Wanner, 2006).

Electronic Cigarettes

Electronic nicotine delivery systems (ENDS), commonly known as electronic cigarettes, use heat or ultrasound to create a nicotine mist and provide hand-to-mouth action, upper airway sensations, and at least some nicotine (Bullen et al., 2010). ENDS were preferred over four NRTs in a short trial of initial reactions (Schneider et al., 2004). One brand of ENDS reduced cravings and withdrawal more effectively than placebo; however, compared with smoking, the ENDS' plasma nicotine boost was only 10% as large, reduced urges to smoke only half as much, and took twice as long to do so (Bullen et al., 2010). Two other ENDS brands were similar to placebo and inferior to smoking for nicotine pharmacokinetics and craving reduction (Eissenberg, 2010). The vacuum required to puff on an ENDS may be higher than that required to smoke a cigarette (Schneider et al., 2004), although this may vary with technique and between devices.

Metered-Dose Inhalers

The first published study of inhaled nicotine used a pressurized metered-dose inhaler (pMDI) to deliver a dose of 53 µg per puff (two puffs every 30 s), compared with a nonnicotine aerosol, lettuce cigarette, and tobacco cigarette, and determined that the cardiovascular effects of these aerosols were caused by nicotine rather than throat irritation (Herxheimer et al., 1967).

In 2005, a clinical trial compared smoking with a pMDI formulation of nicotine base plus ethanol hydrofluoroalkane-134a (HFA-134a) solution with a high respirable fraction (Andrus, Rhem, Rosenfeld, & Dolovich, 1999; Caldwell et al., 2009). Some of the inhaler's nicotine was absorbed rapidly (via the alveoli), but most was absorbed more slowly (via the oropharynx and upper airway). Compared with smoking, the inhaler's median $C_{\max}$ was 50% as large (12.5 vs. 25.9 ng/ml) and its $T_{\max}$ was 6 versus 3 min. Self-rated satisfaction and reduced urge to smoke were similar for the pMDI and cigarette. The inhaler was aversive and caused a dose-dependent reflex interruption of smooth inspiration.

Novel Devices

More recently, three portable novel devices have been studied, which do not use pMDI technology and thereby avoid the problem of timing the inspiration to match the fast propulsion of particles from the device and the potential adverse health consequences of chronic inhalation of HFA (Alexander, 1995; Blondino & Byron, 1998; Graepel & Alexander, 1991; Leach, 2005; Vinegar, Jepson, Cisneros, Rubenstein, & Brock, 2000). The first publication described the AERx Essence system, which creates an aerosol by forcing the formulation under pressure through microscopic holes (Cipolla et al., 2008; Gonda, Bruisnberg, Mudumba, & Cipolla, 2009; Gonda et al., 1998; Schuster, Rubsamen, Lloyd, & Lloyd, 1997). The Staccatto device electrically heats a film of nicotine solution on a metal plate (Rabinowitz et al., 2004; Timmons et al., 2008). The third device consists of a series of chambers through which air flows and entrains nicotine into an aerosol as it moves turbulently through the chambers (Rose, Rose, Turner, & Murugesan, 2008).

The AERx Essence inhaler (Cipolla et al., 2008; Gonda et al., 1998, 2009; Schuster et al., 1997) provides rapid pulmonary nicotine absorption and reduced cravings. Half the dose is in the fine particle fraction (Cipolla et al., 2008). Its ratio of peripheral: central lung deposition is 70% higher compared with pMDI (Farr et al., 2000). However, it also causes throat irritation, cough, and light-headedness (Gonda et al., 2009). Other disadvantages are requiring a battery, requiring the user to reload the device for every puff, and providing doses in small blister packets, which could be punctured and ingested by children or pets.

A clinical trial of a nicotine pyruvate inhaler (Rose et al., 2008; Rose, Turner, Murugesan, Behm, & Laugesen, 2010) gave subjects 10 inhalations of 10, 20, and 30 μ g nicotine per puff compared with placebo (room air) and Nicorette/Nicotrol vapor inhaler. The 20 and 30 μ g doses, but not the 10 μ g dose, produced greater $C_{\max}$ than the vapor inhaler and placebo. Satisfaction was higher for all pyruvate inhalers compared with placebo, but similar to the vapor inhaler. The 20- μ g inhaler was less harsh than the other treatments. The MMAD was 0.62 μ m, small enough to require 5 s of breath holding to deposit on the terminal bronchi and alveoli. This would be a noticeable change for many smokers. British American Tobacco data suggest that the average breath-hold time is 0.45 s; however, others observed a wider range of 2.0–10.6 s (no mean was reported; Marian et al., 2009; Tobin & Sackner, 1982). Philip Morris International purchased patent rights to the nicotine pyruvate inhaler in May 2011 (Philip Morris, 2011).

Discussion

We have reviewed publications of nicotine inhalation devices and assessed the extent to which they deliver nicotine to the lung and the degree to which they replicate the pharmacokinetics and pharmacodynamics of cigarette smoking. Such devices are likely to be more effective at helping people to quit smoking than current forms of NRT.

The Advantages and Technical Barriers to Pulmonary Nicotine Delivery

To maximize the proportion of nicotine-infused particles that deposit in the lung, the particles must have an MMAD small enough to not impinge on the back of the throat but big enough to settle in terminal bronchi and alveoli rather than simply being exhaled (Newman, Anderson, Byron, Dalby, & Peart, 2009). The peak alveolar deposition occurs for particles with an MMAD of 2–4 μ m (Newman et al., 2009) and may require even smaller particles (1.7–2.7 μ m) depending on inspiration period and flow rate (Heyder, 1982). Nicotine particles in this size range can be made by (a) heating tobacco (by combustion [smoking] or electric heater; Stapleton, Russell, Sutherland, & Feyerabend, 1998), (b) condensing and aggregating vaporized nicotine solutions by electric heater (Bullen et al., 2010; Westenberg, 2009), (c) aerosolizing nicotine solutions by bench-top nebulizer machines, (d) pMDIs (Andrus et al., 1999; Caldwell et al., 2009), (e) air classifiers (de Boer, Hagedoorn, Gjaltema, Goede, & Frijlink, 2003), (f) capillary aerosol generators (Howell, Mariaczyl, & Belastro, 2009; Shen, Hindle, & Byron, 2004), and (g) novel devices (Gonda et al., 2009; Lux & Frecker, 1988a; Rose et al., 2008). Of these devices, the pMDI is currently the cheapest, most portable, and relatively simple and economically practical to manufacture on a large scale.

In order to reach the alveoli, a nicotine aerosol must not prevent deep inspiration by provoking cough or reflex interruption of inspiration. Nicotine causes dose-dependent airway irritation, momentary apnea, and cough by stimulation of C-fiber nerve endings, nAChR's, rapidly adapting receptors, and capsaicin receptors (TRPV1) in the upper and lower airways, the lung, the carotid and aortic bodies, and the mediastinum (Cometto-Muniz & Cain, 1992; Dawes & Comroe, 1954; Lavorini et al., 2007; Lee et al., 2007; Lee, Gerhardstein, Wang, & Burki, 1993; Lee, Gu, & Lin, 2010; Lyall et al., 2007; Sellick & Widdicombe, 1971; Widdicombe, 2009). Activation of these irritant mechanisms in the oropharynx and upper airway causes stinging, burning, piquancy, prickling, freshness, and tingling. The degree to which these sensations are irritating depends on whether users view the sensations as intended or unintended (Cometto-Muniz & Cain, 1992). Indeed, some sensory impact is required for nicotine inhalation to be perceived as satisfying (Rose, Behm, & Levin, 1993; Teague, 1983). Irritation from inhaled nicotine may be limited by (a) reducing the amount that impacts on the oropharynx and upper airway, (b) a distracting flavoring or counterirritant, (c) viewing the irritation as desirable, and (d) coating the nicotine in a nonaversive envelope. Each of these points will be discussed.

The amount of nicotine that impinges on the back of the throat can be limited in three ways. First, by reducing its pH to form a nicotine salt (Keithly, Wayne, Cullen, & Connolly, 2005)

and thereby limiting its concentration in gas form (Lechuga-Ballesteros, Kuo, Yuan, & Bueche, 2006; Pankow, 2001); second, by generating small particles; and third, by coordinating inspiration with the release of nicotine from the inhaler. Coordination can be achieved using a breath-activated inhaler or by adding glycerol and activator orifices to reduce the speed and increase the duration of the pMDI plume (Ganderton et al., 2002). However, cigarette smoke is aversive even after the upper airway has been anesthetized (Lee et al., 1993, 2007), perhaps because nicotine activates irritant C-fiber receptors below the larynx (Lavorini et al., 2007).

Compared with the solid or liquid phase, gas-phase nicotine causes a greater sensory impact on the throat (Ferris Wayne, Connolly, & Henningfield, 2006; Pankow, 2001). The formation of gas-phase nicotine can be minimized with reduced temperature and maintaining pH levels below 7 (Pankow, 2001). Lux and Frecker state (without reference) that nicotine aerosols with neutral pH's are not easily inhaled but at pH 5.5 are readily inhaled into the lungs (Lux & Frecker, 1988a). It is not clear what the relationship is between pH and aversion to nicotine. The only relevant study used a very large dose of nicotine per puff and a large MMAD, potentially confusing irritation from nicotine with pH and particle size effects (Burch et al., 1993). In 2006, Jed Rose wrote that researchers acknowledge that nicotine base aerosols are highly aversive to inhale (Rose, 2006). However, a high pH and throat scratch are rewarding for some smokers (Teague, 1983).

There are further advantages to reducing the pH of nicotine to match the lung's extravascular fluid pH = 6.69 ± 0.07 (Effros & Chinard, 1969). It avoids alkaline activation of protective mechanisms located in the airway and carotid bodies, and it prevents alkaline damage to cells lining the airway. Nicotine salts are polar and cannot immediately cross plasma membranes, unlike the nonpolar, lipid-soluble freebase. Before nicotine salt molecules can gain entry to a cell, they must first dissociate into the freebase and acid, and then the freebase can gain entry. This process occurs in about the time it takes for the cell's cytoplasm to buffer its pH, and hence, nicotine salt exposure does not abruptly alter the cell's pH.

A nicotine inhaler may be less harsh if flavorings and counterirritants are added to its formulation. Flavoring agents used in cigarettes include liquorice, vanilla, and citrus flavors (Baker, Pereira da Silva, & Smith, 2004). Flavorings are also used in aerosol medicines, such as vanillin in nebuluses of the bitter alkaloid ipratropium bromide (Atrovent; Conkins, Economou, Boersma, Dedhiya, & Hansen, 1999). Menthol in cigarettes is a counterirritant that makes the smoke less aversive and produces a transient apnea, which increases pulmonary absorption (Wayne & Connolly, 2004). Menthol was also added to the Nicotrol/Nicorette inhaler (Schneider et al., 2001) and a pMDI formulation (Caldwell et al., 2009). A person's attitude toward an aversive respiratory sensation can modify their cough reflex in response to it (Cometto-Muniz & Cain, 1992; Lavorini et al., 2007). Flavoring the nicotine inhaler may help people to view its sensory qualities as desirable and thereby suppress coughing.

Coating nicotine-bearing particles with a nonirritating substance may reduce aversion. In cigarettes, nicotine is dissolved in particles of tar, which may reduce airway irritation by minimizing gas-phase nicotine (Rose & Behm, 1987; Rose,

Behm, Westman, & Coleman, 1999; Rose, Westman, Behm, Johnson, & Goldberg, 1999). It may be possible to coat nicotine in a pMDI formulation with glycerol, propylene glycol, or complex sugar molecules, such as beta-cyclodextrin, although this may increase the particle size and lung residency time (Brambilla et al., 1999; Cabral Marques, Hadgraft, Kellaway, & Taylor, 1991; Nakate et al., 2003; Prigal, McGavack, Speer, & Harris, 1947).

The Advantages and Disadvantages of Inhaler Devices Identified in This Review

The devices identified in this review varied in their ability to mimic the pulmonary delivery of cigarette smoking and their portability. Trials of bulky nebulizer devices demonstrated that they were capable of pulmonary delivery and achieved reasonable plasma levels if the pH of the nicotine was reduced and the particle sizes were small; however, their usefulness is limited by their lack of portability. The most widely available portable inhaler (Nicotrol/Nicorette/Favor/Pharmacia inhaler) had a slower pharmacokinetic profile than cigarettes or the other inhalers identified in the present review. Despite its nonpulmonary delivery route, a Cochrane review found that the relative risk of 6-month abstinence with this oral inhaler was 1.90 (95% *CI* = 1.36–2.67; Stead et al., 2008), which suggests that the oral inhaler is effective as a smoking cessation medication despite having a slower pharmacokinetic profile than cigarettes.

Like the oral inhaler, ENDS are also widely available. Considerable experience and practice is required to learn to puff ENDS frequently in order to absorb enough nicotine to quench the urge to smoke (Trehay et al., 2011). Novice users may account for why some studies have observed a slow, low-dose pharmacokinetic profile (Eissenberg, 2010). Experienced users report quickly reduced urges to smoke and minimal withdrawal symptoms and weight gain. These observations, along with high salivary cotinine measurements in experienced users (Etter & Bullen, 2011), suggest that vapors can rapidly absorb nicotine in daily quantities comparable to smokers. No serious side effects have been reported yet, although allergic reactions to the vehicle may occur. Flavored glycerin or propylene glycol aerosols are typical and avoid irritation. Unlike users of other NRTs, ENDS users are inspired to spontaneously form social networks devoted to the promotion of ENDS as a safer alternative to smoking (McQueen, Tower, & Sumner, 2011). This social phenomenon is a uniquely strong endorsement of the technology as a commercially viable alternative to smoking.

Other portable devices identified in this review were not currently commercially available, such as the AERx Essence inhaler, the nicotine pyruvate inhaler, and pMDI devices. Of these devices, the AERx Essence had a much higher C_{max} (Supplementary Table 3) and superior particle size distribution. Both the AERx Essence and nicotine pyruvate inhaler had a very short arterial T_{max} , which indicates that most of the nicotine was absorbed in the peripheral pulmonary zones. The C_{max} of the pMDI was higher than the nicotine pyruvate inhaler but lower than the AERx Essence (Table 3). The pMDI's larger MMAD, high pH, and its aversive side effects explain why it had a longer T_{max} than the AERx and pyruvate inhalers. Exhalation of the very small particles of nicotine pyruvate and the extremely low dose per puff were probably responsible for the low C_{max} of the pyruvate inhaler. Whether or not higher doses of nicotine pyruvate per puff would be tolerable needs to be explored. All these three inhalers have the

potential to rival the pharmacokinetics of smoking, although their ability to match the pharmacodynamics of smoking and their capacity to act as smoking cessation aids needs to be tested in randomized controlled trials.

Potential Therapeutic Role of Nicotine Inhalers

Nicotine inhalers would be useful to treat other conditions in addition to tobacco dependence. Nicotine has therapeutic effects that are important for some people. Nicotine enhances cognition, in both smokers and nonsmokers, and does so even in smokers who are not experiencing withdrawal symptoms (Heishman, Kleykamp, & Singleton, 2010; Marchant, Trawley, & Rusted, 2008; Myers, Taylor, Moolchan, & Heishman, 2008). The cognitive effects of nicotine may ameliorate attention deficit hyperactivity disorder and Alzheimer's disease (Levin & Rezvani, 2002; Levin et al., 1996; Vagg & Chapman, 2005). Improvements in cognitive function may explain the high prevalence of smoking among people with psychiatric disorders such as schizophrenia (Mobascher & Winterer, 2008). Also, nicotine has anti-inflammatory properties (Kalra et al., 2004) and is helpful in managing ulcerative colitis (Birrenbach & Bocker, 2004; McGrath, McDonald, & Macdonald, 2004). Smokers may want a substitute for the social and relaxation roles that cigarettes fulfill (Ennett et al., 2010; Fry, Grogan, Gough, & Conner, 2008; Kahler, Daughters, Leventhal, Gwaltney, & Palfai, 2007; Ritchie, Amos, & Martin, 2010).

Future Directions

Before large clinical trials are conducted, the performance of the pMDI and the pyruvate inhalers needs to be refined. The pMDI may be improved by use of a nicotine salt, an appropriate spacer device, and flavorings. Nicotine pMDIs may be improved further by use of a spacer device to ensure that the vapor can be puffed on like a cigarette, avoiding the high-velocity jet of a pMDI. A spacer may provide some resistance to airflow to open the architecture of the throat so fewer particles impact in the pharynx (Newman et al., 2009). Both the pyruvate and the AERx inhalers need to be made smaller and portable, and the potential to increase the dose of the pyruvate inhaler needs to be tested. Further research is required to better understand the role of pH, flavorings, counterirritants, the nonnicotine rewarding components of tobacco smoke, and nonaversive vehicles in maximizing pulmonary delivery of medicinal nicotine. Other ingredients of cigarette smoke (harman, norharman, anabaine, and anatabine) could enhance reinforcement (Clemens, Caille, Stinus, & Cador, 2009; Herraiz & Chaparro, 2005; Lewis, Miller, & Lea, 2007), but some of these potential additives may not be as safe as nicotine (Jimenez, Riveron-Negrete, Abdullaev, Espinosa Aguirre, & Rodriguez Arnaiz, 2008; Keeler, Crowe, & Lambert, 1984; Nakagawa, Suzuki, Ishii, Ogata, & Nakae, 2010).

Corporations are unlikely to risk investing in research and design programs to develop tolerable effective pulmonary delivery devices under very risk-averse regulatory environments because of concerns about the safety of nicotine and its addictive potential (Sweanor, 2000). For example, conventional Western manufacturers have not brought to market devices such as Altria's Chrysalis inhaler (Anonymous, 2008) or Next Safety's nicotine inhaler (Next Safety, 2011).

The potential risks of chronic nicotine inhalation are far lower than the risks of continued smoking. Although nicotine may have adverse cardiovascular effects and may be a co-mutagen (Benowitz, 1993b; Cooke & Bitterman, 2004; Dasgupta & Chellappan, 2006; Heesch et al., 2001), NRT is safe in people with cardiovascular disease (Balfour et al., 2000), NRT does not increase the risk of cancer (Murray, Connett, & Zapawa, 2009), and after decades of experience NRTs have a good safety track record (Balfour et al., 2000). The risks of long-term NRT use are far outweighed by the risks of long-term addiction to smoking (Apelberg et al., 2010; Fagerström, 2002; Sumner, 2003; Sweanor, 1999; Warner et al., 1997). Specific concerns about ENDS have led to calls for tighter regulation of ENDS availability (Cobb & Abrams, 2011). Although HFA propellants can produce cardiac sensitization, they appear to be safe at typical therapeutic levels in pMDIs (Donnell et al., 1995; Harrison et al., 1996). On balance, it is unlikely that nicotine inhalers will cause significant health problems.

Smoking is an exceptionally common, risky, and persistent behavior with staggering costs in terms of human suffering. NRT is relatively ineffective—current smokers are unable or unwilling to quit despite extensive education and public health initiatives. For these smokers, inhaled nicotine could be very attractive and even life-saving.

Consumers may or may not accept a pMDI as an alternative to cigarettes or ENDS. pMDI users cannot display emotion in social settings as they do with cigarettes and ENDS. The pensive preparation to partake, the intense puffs of concentration, or a long contented draft conveniently convey moods in a way that asthma inhalers do not. On the other hand, pMDIs may be more convenient to use than ENDS because pMDIs contain more doses per canister and have no battery to recharge. Consumer acceptance is not guaranteed, but the greater the variety of rapid nicotine delivery devices the greater the chance that smokers will find a device that suits them. The health consequence of giving consumers another nicotine maintenance alternative to cigarettes should be favorable.

The present review has limitations: only a small number of nicotine inhalation devices have been developed and tested and the review focused on clinical trials and therefore did not take account of preclinical inhaler trials. The strength of this review is that it is the first review that we are aware of that has drawn together the diverse range of information on nicotine inhalation devices that is scattered throughout the literature.

This review has contributed to the literature by summarizing the benefits and technical issues relating to nicotine inhalation and has shown that an effective, tolerable, pulmonary nicotine delivery device may be more effective than current NRTs. Its development would be a complex undertaking and requires investment and a supportive regulatory environment. Further research is required to maximize alveolar delivery. Investment in development of therapeutic pulmonary nicotine devices is likely to result in a major advance in smoking cessation treatment and prevent considerable mortality and morbidity.

Supplementary Material

Supplementary Tables 1–3 and Supplementary Figure 1 can be found online at <http://www.ntr.oxfordjournals.org/>.

Funding

This work was supported by the Health Research Council of New Zealand.

Declaration of Interests

None declared.

Acknowledgments

We gratefully acknowledge the helpful comments of Paul Andrus.

References

- Alexander, D. J. (1995). Safety of propellants. *Journal of Aerosol Medicine*, 8(Suppl. 1), S29–S34.
- Andrus, P. G., Rhem, R., Rosenfeld, J., & Dolovich, M. B. (1999). Nicotine microaerosol inhaler. *Canadian Respiratory Journal*, 6, 509–512.
- Anonymous, (2008). Discovery labs and Chrysalis technologies modify collaboration for future development of aerosolized drug device products. *Drug Discovery Online*, Retrieved from <http://www.webcitation.org/5zIsI7AFP>
- Apelberg, B. J., Onicescu, G., Avila-Tang, E., & Samet, J. M. (2010). Estimating the risks and benefits of nicotine replacement therapy for smoking cessation in the United States. *American Journal of Public Health*, 100, 341–348. doi:10.2105/AJPH.2008.147223
- Armitage, A. K., Dollery, C. T., George, C. F., Houseman, T. H., Lewis, P. J., & Turner, D. M. (1975). Absorption and metabolism of nicotine from cigarettes. *British Medical Journal*, 4, 313–316.
- Baker, R. R., Pereira da Silva, J., & Smith, G. (2004). The effect of tobacco ingredients on smoke chemistry. Part I: Flavourings and additives. *Food and Chemical Toxicology*, 42(Suppl.), S3–S37. doi:10.1016/S0278-6915(03)00189-3
- Balfour, D., Benowitz, N., Fagerström, K., Kunze, M., & Keil, U. (2000). Diagnosis and treatment of nicotine dependence with emphasis on nicotine replacement therapy. A status report. *European Heart Journal*, 21, 438–445. doi:10.1053/euhj.1999.1949
- Balfour, D. J. K. (2004). The neurobiology of tobacco dependence: A preclinical perspective on the role of the dopamine projections to the nucleus. *Nicotine & Tobacco Research*, 6, 899–912. doi:10.1080/14622200412331324965
- Bansal, M. A., Cummings, K. M., Hyland, A., & Giovino, G. A. (2004). Stop-smoking medications: Who uses them, who misuses them, and who is misinformed about them? *Nicotine & Tobacco Research*, 6(Suppl. 3), S303–S310. doi:10.1053/euhj.1999.1949
- Barrett, S. P. (2010). The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers. *Behavioural Pharmacology*, 21, 144–152. doi:10.1097/FBP.0b013e328337be68
- Benowitz, N. L. (1993a). Clinical pharmacology and toxicology of cocaine. *Pharmacology & Toxicology*, 72, 3–12.
- Benowitz, N. L. (1993b). Smoking-induced coronary vasoconstriction: Implications for therapeutic use of nicotine. *Journal of the American College of Cardiology*, 22, 648–649.
- Benowitz, N. L. (2008). Neurobiology of nicotine addiction: Implications for smoking cessation treatment. *American Journal of Medicine*, 121(4 Suppl. 1), S3–S10. doi:10.1016/j.amjmed.2008.01.015
- Benowitz, N. L., & Gourlay, S. G. (1997). Cardiovascular toxicity of nicotine: Implications for nicotine replacement therapy. *Journal of the American College of Cardiology*, 29, 1422–1431.
- Best, J. A., & Hakstian, A. R. (1978). A situation-specific model for smoking behavior. *Addictive Behaviors*, 3, 79–92.
- Birrenbach, T., & Bocker, U. (2004). Inflammatory bowel disease and smoking: A review of epidemiology, pathophysiology, and therapeutic implications. *Inflammatory Bowel Diseases*, 10, 848–859. doi:10.1097/00054725-200411000-00019
- Blondino, F. E., & Byron, P. R. (1998). Surfactant dissolution and water solubilization in chlorine-free liquified gas propellants. *Drug Development and Industrial Pharmacy*, 24, 935–945.
- Bolliger, C. T., Van Biljon, X., & Axelsson, A. (2007). A nicotine mouth spray for smoking cessation: A pilot study of preference, safety and efficacy. *Respiration*, 74, 196–201. doi:10.1159/000097136
- Bolliger, C. T., Zellweger, J. P., Danielsson, T., Van Biljon, X., Robidou, A., Westin, A., et al. (2000). Smoking reduction with oral nicotine inhalers: Double blind, randomised clinical trial of efficacy and safety. *British Medical Journal*, 321, 329–333. doi:10.1136/bmj.321.7257.329
- Brambilla, G., Ganderton, D., Garzia, R., Lewis, D., Meakin, B., & Ventura, P. (1999). Modulation of aerosol clouds produced by pressurised inhalation aerosols. *International Journal of Pharmaceutics*, 186, 53–61.
- Bullen, C., McRobbie, H., Thornley, S., Glover, M., Lin, R., & Laugesen, M. (2010). Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: Randomised cross-over trial. *Tobacco Control*, 19, 98–103. doi:10.1136/tc.2009.031567
- Burch, S. G., Erbland, M. L., Gann, L. P., & Hiller, F. C. (1989). Plasma nicotine levels after inhalation of aerosolized nicotine. *American Review of Respiratory Disease*, 140, 955–957.
- Burch, S. G., Gann, L. P., Olsen, K. M., Anderson, P. J., Hiller, F. C., & Erbland, M. L. (1993). Effect of pH on nicotine absorption

- and side effects produced by aerosolized nicotine. *Journal of Aerosol Medicine Deposition, Clearance, and Effects in the Lung*, 6, 45–52.
- Cabral Marques, H. M., Hadgraft, J., Kellaway, I. W., & Taylor, G. (1991). Studies of cyclodextrin inclusion complexes. III. The pulmonary absorption of [beta]-, DM-[beta]- and HP-[beta]-cyclodextrins in rabbits. *International Journal of Pharmaceutics*, 77, 297–302. doi:10.1016/0378-5173(91)90330-q
- Caldwell, B., Burgess, C., & Crane, J. (2010). Randomized crossover trial of the acceptability of snus, nicotine gum, and Zonnic therapy for smoking reduction in heavy smokers. *Nicotine & Tobacco Research*, 12, 179–183. doi:10.1093/ntr/ntp189
- Caldwell, B., Dickson, S., Burgess, C., Siebers, R., Mala, S., Parkes, A., et al. (2009). A pilot study of nicotine delivery to smokers from a metered dose inhaler. *Nicotine & Tobacco Research*, 11, 342–347. doi:10.1093/ntr/ntp027
- Cipolla, D. C., Bruninenberg, P., Eliahu, P., Johansson, E., Marjason, J. K., Morishige, R. J., et al. (2008). Development of an inhaled AERx Essence nicotine product for smoking cessation. *Respiratory Drug Delivery Europe*, 2, 365–370. Retrieved from <http://www.rddonline.com>
- Clemens, K. J., Caille, S., Stinus, L., & Cadot, M. (2009). The addition of five minor tobacco alkaloids increases nicotine-induced hyperactivity, sensitization and intravenous self-administration in rats. *International Journal of Neuropsychopharmacology*, 12, 1355–1366. doi:10.1017/S1461145709000273
- Cobb, N. K., & Abrams, D. B. (2011). E-cigarette or drug-delivery device? Regulating novel nicotine products. *New England Journal of Medicine*, 365, 193–195. doi:10.1056/NEJMp1105249
- Cometto-Muniz, J. E., & Cain, W. S. (1992). Sensory irritation. Relation to indoor air pollution. *Annals of the New York Academy of Sciences*, 641, 137–151.
- Conkins, D., Economou, J. E., Boersma, J. A., Dedhiya, M. G., & Hansen, G. (1999). Reversed phase-high performance liquid chromatographic (RP-HPLC) method to measure migration of semi-volatile compound, vanillin, in ipratropium bromide inhalation solution. *Aaps Pharm Sci*, 1, E15.
- Cooke, J. P., & Bitterman, H. (2004). Nicotine and angiogenesis: A new paradigm for tobacco-related diseases. *Annals of Medicine*, 36, 33–40. doi:10.1080.07853890310017576
- Croghan, I. T., Hurt, R. D., Dakhil, S. R., Croghan, G. A., Sloan, J. A., Novotny, P. J., et al. (2007). Randomized comparison of a nicotine inhaler and bupropion for smoking cessation and relapse prevention. *Mayo Clinic Proceedings*, 82, 186–195. doi:10.4065/82.2.186
- Croghan, I. T., Hurt, R. D., Ebbert, J. O., Croghan, G. A., Polk, O. D., Jr., Stella, P. J., et al. (2010). Racial differences in smoking abstinence rates in a multicenter, randomized, open-label trial in the United States. *Journal of Public Health*, 18, 59–68. doi:10.1007/s10389-009-0277-2
- Cummings, K. M., & Hyland, A. (2005). Impact of nicotine replacement therapy on smoking behavior. *Annual Review of Public Health*, 26, 583–599. doi:10.1146/annurev.publhealth.26.021304.144501
- Dar, R., & Frenk, H. (2007). Reevaluating the nicotine delivery kinetics hypothesis. *Psychopharmacology*, 192, 1–7. doi:10.1007/s00213-007-0768-1
- Darredeau, C., & Barrett, S. P. (2010). The role of nicotine content information in smokers' subjective responses to nicotine and placebo inhalers. *Human Psychopharmacology*, 25, 577–581. doi:10.1002/hup.1159
- Dasgupta, P., & Chellappan, S. P. (2006). Nicotine-mediated cell proliferation and angiogenesis: New twists to an old story. *Cell Cycle*, 5, 2324–2328. doi:10.4161/cc.5.20.3366
- Dawes, G. S., & Comroe, J. H., Jr. (1954). Chemoreflexes from the heart and lungs. *Physiological Reviews*, 34, 167–201.
- de Boer, A. H., Hagedoorn, P., Gjaltema, D., Goede, J., & Frijlink, H. W. (2003). Air classifier technology (ACT) in dry powder inhalation. Part 1. Introduction of a novel force distribution concept (FDC) explaining the performance of a basic air classifier on adhesive mixtures. *International Journal of Pharmaceutics*, 260, 187–200. doi:10.1016/S0378-5173(03)00250-3
- de Wit, H., Bodker, B., & Ambre, J. (1992). Rate of increase of plasma drug level influences subjective response in humans. *Psychopharmacology*, 107, 352–358.
- Donnell, D., Harrison, L. I., Ward, S., Klinger, N. M., Ekholm, B. P., Cooper, K. M., et al. (1995). Acute safety of the CFC-free propellant HFA-134a from a pressurized metered dose inhaler. *European Journal of Clinical Pharmacology*, 48, 473–477.
- Dunbar, M. S., Scharf, D., Kirchner, T., & Shiffman, S. (2010). Do smokers crave cigarettes in some smoking situations more than others? Situational correlates of craving when smoking. *Nicotine & Tobacco Research*, 12, 226–234. doi:10.1093/ntr/ntp198
- Effros, R. M., & Chinard, F. P. (1969). The in vivo pH of the extravascular space of the lung. *Journal of Clinical Investigation*, 48, 1983–1996.
- Eissenberg, T. (2010). Electronic nicotine delivery devices: Ineffective nicotine delivery and craving suppression after acute administration. *Tobacco Control*, 19, 87–88. doi:10.1136/tc.2009.033498
- Ennett, S. T., Foshee, V. A., Bauman, K. E., Hussong, A., Faris, R., Hipp, J. R., et al. (2010). A social contextual analysis of youth cigarette smoking development. *Nicotine & Tobacco Research*, 12, 950–962. doi:10.1093/ntr/ntp122
- Etter, J. F., & Bullen, C. (2011). Saliva cotinine levels in users of electronic cigarettes. *European Respiratory Journal*, 38, 1219–1220. doi:10.1183/09031936.00066011
- Etter, J. F., & Stapleton, J. A. (2006). Nicotine replacement therapy for long-term smoking cessation: A meta-analysis. *Tobacco Control*, 15, 280–285. doi:10.1136/tc.2005.015487
- Fagerström, K. (2002). Quit or die: Nothing in between? *Respiration*, 69, 387–388. doi:10.1159/000064017

- Fagerström, K. O., Hughes, J. R., Rasmussen, T., & Callas, P. W. (2000). Randomised trial investigating effect of a novel nicotine delivery device (Eclipse) and a nicotine oral inhaler on smoking behaviour, nicotine and carbon monoxide exposure, and motivation to quit. *Tobacco Control*, 9, 327–333. doi:10.1136/tc.9.3.327
- Fagerström, K. O., Tejdin, R., Westin, A., & Lunell, E. (1997). Aiding reduction of smoking with nicotine replacement medications: Hope for the recalcitrant smoker? *Tobacco Control*, 6, 311–316.
- Farr, S. J., Warren, S. J., Lloyd, P., Okikawa, J. K., Schuster, J. A., Rowe, A. M., et al. (2000). Comparison of in vitro and in vivo efficiencies of a novel unit-dose liquid aerosol generator and a pressurized metered dose inhaler. *International Journal of Pharmaceutics*, 198, 63–70. doi:10.1016/S0378-5173(99)00452-4
- Ferris Wayne, G., Connolly, G. N., & Henningfield, J. E. (2006). Brand differences of free-base nicotine delivery in cigarette smoke: The view of the tobacco industry documents. *Tobacco Control*, 15, 189–198. doi:10.1136/tc.2005.013805
- File, S. E., Fluck, E., & Leahy, A. (2001). Nicotine has calming effects on stress-induced mood changes in females, but enhances aggressive mood in males. *International Journal of Neuropsychopharmacology*, 4, 371–376. doi:10.1017/S1461145701002577
- Fry, G., Grogan, S., Gough, B., & Conner, M. (2008). Smoking in the lived world: How young people make sense of the social role cigarettes play in their lives. *British Journal of Social Psychology*, 47, 763–780. doi:10.1348/014466608X288818
- Ganderton, D., Lewis, D., Davies, R., Meakin, B., Brambilla, G., & Church, T. (2002). Modulite: A means of designing the aerosols generated by pressurized metered dose inhalers. *Respiratory Medicine*, 96(Suppl. D), S3–S8. doi:10.1016/S0954-6111(02)80018-X
- Glaulier, S. (2004). Measures and models of nicotine dependence: Positive reinforcement. *Addiction*, 99(Suppl. 1), 30–50. doi:10.1111/j.1360-0443.2004.00736.x
- Gonda, I. (2006). Systemic delivery of drugs to humans via inhalation. *Journal of Aerosol Medicine Deposition, Clearance, and Effects in the Lung*, 19, 47–53. doi:10.1089/jam.2006.19.47
- Gonda, I., Bruisnberg, P., Mudumba, S., & Cipolla, D. (2009). Smoking cessation approach via deep lung delivery of 'Clean' nicotine. *Respiratory Drug Delivery Europe*, 1, 57–62. Retrieved from <http://www.rddonline.com>
- Gonda, I., Schuster, J. A., Rubsamen, R. M., Lloyd, P., Cipolla, D., & Farr, S. J. (1998). Inhalation delivery systems with compliance and disease management capabilities. *Journal of Controlled Release*, 53, 269–274. doi:10.1016/S0168-3659(98)00260-5
- Graepel, P., & Alexander, D. J. (1991). CFC replacements: Safety testing, approval for use in metered dose inhalers. *Journal of Aerosol Medicine*, 4, 193–200.
- Gray, N., Henningfield, J. E., Benowitz, N. L., Connolly, G. N., Dresler, C., Fagerström, K., et al. (2005). Toward a comprehensive long term nicotine policy. *Tobacco Control*, 14, 161–165. doi:10.1136/tc.2004.010272
- Hajek, P., West, R., Foulds, J., Nilsson, F., Burrows, S., & Meadow, A. (1999). Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Archives of Internal Medicine*, 159, 2033–2038.
- Hand, S., Edwards, S., Campbell, I. A., & Cannings, R. (2002). Controlled trial of three weeks nicotine replacement treatment in hospital patients also given advice and support. *Thorax*, 57, 715–718. doi:10.1136/thorax.57.8.715
- Hansson, L., Choudry, N. B., Karlsson, J. A., & Fuller, R. W. (1994). Inhaled nicotine in humans: Effect on the respiratory and cardiovascular systems. *Journal of Applied Physiology*, 76, 2420–2427.
- Harrison, L. I., Donnell, D., Simmons, J. L., Ekholm, B. P., Cooper, K. M., & Wyld, P. J. (1996). Twenty-eight-day double-blind safety study of an HFA-134a inhalation aerosol system in healthy subjects. *Journal of Pharmacy and Pharmacology*, 48, 596–600.
- Hatsukami, D. K., Morgan, S. F., Pickens, R. W., & Champagne, S. E. (1990). Situational factors in cigarette smoking. *Addictive Behaviors*, 15, 1–12.
- Heeschen, C., Jang, J. J., Weis, M., Pathak, A., Kaji, S., Hu, R. S., et al. (2001). Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. *Nature Medicine*, 7, 833–839. doi:10.1038/89961
- Heishman, S. J., Kleykamp, B. A., & Singleton, E. G. (2010). Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology*, 210, 453–469. doi:10.1007/s00213-010-1848-1
- Henningfield, J. E. (1987). Reducing the urge to smoke. *Chest*, 92, 963.
- Henningfield, J. E., Fant, R. V., Gitchell, J., & Shiffman, S. (2000). Tobacco dependence. Global public health potential for new medications development and indications. *Annals of the New York Academy of Sciences*, 909, 247–256. doi:10.1111/j.1749-6632.2000.tb06686.x
- Henningfield, J. E., & Keenan, R. M. (1993). Nicotine delivery kinetics and abuse liability. *Journal of Consulting and Clinical Psychology*, 61, 743–750.
- Henningfield, J. E., London, E. D., & Benowitz, N. L. (1990). Arterial-venous differences in plasma concentrations of nicotine after cigarette smoking. *Journal of the American Medical Association*, 263, 2049–2050.
- Henningfield, J. E., Stapleton, J. M., Benowitz, N. L., Grayson, R. F., & London, E. D. (1993). Higher levels of nicotine in arterial than in venous blood after cigarette smoking. *Drug and Alcohol Dependence*, 33, 23–29.
- Herning, R. I., Jones, R. T., Benowitz, N. L., & Mines, A. H. (1983). How a cigarette is smoked determines blood nicotine levels. *Clinical Pharmacology and Therapeutics*, 33, 84–90.
- Herraziz, T., & Chaparro, C. (2005). Human monoamine oxidase is inhibited by tobacco smoke: Beta-carboline alkaloids act

- as potent and reversible inhibitors. *Biochemical and Biophysical Research Communications*, 326, 378–386. doi:10.1016/j.bbrc.2004.11.033
- Herxheimer, A., Griffiths, R. L., Hamilton, B., & Wake, M. (1967). Circulatory effects of nicotine aerosol inhalations and cigarette smoking in man. *Lancet*, 2, 754–755.
- Heyder, J. (1982). Alveolar deposition of inhaled particles in humans. *American Industrial Hygiene Association Journal*, 43, 864–866.
- Hjalmarson, A., Nilsson, F., Sjostrom, L., & Wiklund, O. (1997). The nicotine inhaler in smoking cessation. *Archives of Internal Medicine*, 157, 1721–1728.
- Howell, T., Mariaczyl, C., & Belastro, M. (2009). *Heat capacitor for capillary aerosol generator, United States of America Patent No. US 7,518,123 B2*. United States Patent and Trademark Office. Retrieved from <http://patft.uspto.gov/>
- Hughes, J. R. (1993). Pharmacotherapy for smoking cessation: Unvalidated assumptions, anomalies, and suggestions for future research. *Journal of Consulting and Clinical Psychology*, 61, 751–760.
- Hughes, J. R. (2001). Why does smoking so often produce dependence? A somewhat different view. *Tobacco Control*, 10, 62–64. doi:10.1136/tc.10.1.62
- Institute of Medicine. (2001). Clearing the smoke: Assessing the science base for tobacco harm reduction. Retrieved from <http://www.nap.edu/>. doi:10.1111/j.1520-037X.2003.01377.x
- Jimenez, J., Riveron-Negrete, L., Abdullaev, F., Espinosa-Aguirre, J., & Rodriguez-Arnaiz, R. (2008). Cytotoxicity of the beta-carboline alkaloids harmine and harmaline in human cell assays in vitro. *Experimental and Toxicologic Pathology*, 60, 381–389. doi:10.1016/j.etp.2007.12.003
- Kahler, C. W., Daughters, S. B., Leventhal, A. M., Gwaltney, C. J., & Palfai, T. P. (2007). Implicit associations between smoking and social consequences among smokers in cessation treatment. *Behaviour Research and Therapy*, 45, 2066–2077. doi:10.1016/j.brat.2007.03.004
- Kalra, R., Singh, S. P., Pena-Philippides, J. C., Langley, R. J., Razani Boroujerdi, S., & Sopori, M. L. (2004). Immunosuppressive and anti-inflammatory effects of nicotine administered by patch in an animal model. *Clinical and Diagnostic Laboratory Immunology*, 11, 563–568. doi:10.1128/CDLI.11.3.563–568.2004
- Keeler, R. F., Crowe, M. W., & Lambert, E. A. (1984). Teratogenicity in swine of the tobacco alkaloid anabasine isolated from *Nicotiana glauca*. *Teratology*, 30, 61–69.
- Keithly, L., Wayne, G. F., Cullen, D. M., & Connolly, G. N. (2005). Industry research on the use and effects of levulinic acid: A case study in cigarette additives. *Nicotine & Tobacco Research*, 7, 761–771. doi:10.1080/14622200500259820
- Lavorini, F., Pantaleo, T., Geri, P., Mutolo, D., Pistolesi, M., & Fontana, G. A. (2007). Cough and ventilatory adjustments evoked by aerosolised capsaicin and distilled water (fog) in man. *Respiratory Physiology & Neurobiology*, 156, 331–339. doi:10.1016/j.resp.2006.10.006
- Le Houezec, J. (1998). Nicotine: Abused substance and therapeutic agent. *Journal of Psychiatry & Neuroscience*, 23, 95–108.
- Leach, C. L. (2005). The CFC to HFA transition and its impact on pulmonary drug development. *Respiratory Care*, 50, 1201–1208. Retrieved from <http://www.rcjournal.com/>
- Leach, C. L. (2007). Inhalation aspects of therapeutic aerosols. *Toxicologic Pathology*, 35, 23–26. doi:10.1080/01926230601072335
- Lechuga-Ballesteros, D., Kuo, M.-C., Yuan, S., & Bueche, B. (2006). *Aerosolizable formulation comprising nicotine, United States Patent No. 2006/0018840 A1*. United States Patent and Trademark Office, Retrieved from <http://patft.uspto.gov/>
- Lee, L.-Y., Burki, N. K., Gerhardstein, D. C., Gu, Q., Kou, Y. R., & Xu, J. (2007). Airway irritation and cough evoked by inhaled cigarette smoke: Role of neuronal nicotinic acetylcholine receptors. *Pulmonary Pharmacology and Therapeutics*, 20, 355–364. doi:10.1016/j.pupt.2006.10.007
- Lee, L.-Y., Gerhardstein, D. C., Wang, A. L., & Burki, N. K. (1993). Nicotine is responsible for airway irritation evoked by cigarette smoke inhalation in men. *Journal of Applied Physiology*, 75, 1955–1961.
- Lee, L.-Y., Gu, Q., & Lin, Y.-S. (2010). Effect of smoking on cough reflex sensitivity: Basic and preclinical studies. *Lung*, 188(Suppl. 1), S23–S27. doi:10.1007/s00408-009-9191-1
- Levin, E. D., Conners, C. K., Sparrow, E., Hinton, S. C., Erhardt, D., Meck, W. H., et al. (1996). Nicotine effects on adults with attention deficit/hyperactivity disorder. *Psychopharmacology*, 123, 55–63.
- Levin, E. D., & Rezvani, A. H. (2002). Nicotinic treatment for cognitive dysfunction. *Current Drug Targets—CNS and Neurological Disorders*, 1, 423–431. doi:10.1016/j.ntt.2005.12.010
- Levy, D. T., Mabry, P. L., Graham, A. L., Orleans, C. T., & Abrams, D. B. (2010). Exploring scenarios to dramatically reduce smoking prevalence: A simulation model of the three-part cessation process. *American Journal of Public Health*, 100, 1253–1259. Retrieved from <http://dx.doi.org/10.2105/AJPH.2009.166785>
- Lewis, A., Miller, J. H., & Lea, R. A. (2007). Monoamine oxidase and tobacco dependence. *Neurotoxicology*, 28, 182–195. doi:10.1016/j.neuro.2006.05.019
- Lunell, E., Bergstrom, M., Antoni, G., Langstrom, B., & Nordberg, A. (1996). Nicotine deposition and body distribution from a nicotine inhaler and a cigarette studied with positron emission tomography. *Clinical Pharmacology and Therapeutics*, 59, 593–594.
- Lunell, E., Molander, L., Ekberg, K., & Wahren, J. (2000). Site of nicotine absorption from a vapour inhaler—comparison with cigarette smoking. *European Journal of Clinical Pharmacology*, 55, 737–741. doi:10.1007/s002280050007
- Lunell, E., Molander, L., Leischow, S. J., & Fagerström, K.-O. (1995). Effect of nicotine vapour inhalation on the relief of

- tobacco withdrawal symptoms. *European Journal of Clinical Pharmacology*, 48, 235–240.
- Lux, J. E., & Frecker, R. C. (1988a). Generation of a submicrometre nicotine aerosol for inhalation. *Medical & Biological Engineering & Computing*, 26, 232–234.
- Lux, J. E., & Frecker, R. C. (1988b). Subjective responses to inhaled and intravenous injected nicotine. *Clinical Pharmacology and Therapeutics*, 43, 186.
- Lyall, V., Phan, T.-H.T., Mummalaneni, S., Mansouri, M., Heck, G. L., Kobal, G., et al. (2007). Effect of nicotine on chorda tympani responses to salty and sour stimuli. *Journal of Neurophysiology*, 98, 1662–1674. doi:10.1152/jn.00366.2007
- Marchant, N. L., Trawley, S., & Rusted, J. M. (2008). Prospective memory or prospective attention: Physiological and pharmacological support for an attentional model. *International Journal of Neuropsychopharmacology*, 11, 401–411. doi:10.1017/S146114570700819X
- Marian, C., O'Connor, R. J., Djordjevic, M. V., Rees, V. W., Hatsukami, D. K., & Shields, P. G. (2009). Reconciling human smoking behavior and machine smoking patterns: Implications for understanding smoking behavior and the impact on laboratory studies. *Cancer Epidemiology, Biomarkers & Prevention*, 18, 3305–3320. doi:10.1158/1055-9965.EPI-09-1014
- McGrath, J., McDonald, J. W. D., & Macdonald, J. K. (2004). Transdermal nicotine for induction of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews*, (4). CD004722. doi:10.1002/14651858.CD004722.pub2
- McNeill, A., Foulds, J., & Bates, C. (2001). Regulation of nicotine replacement therapies (NRT): A critique of current practice. *Addiction*, 96, 1757–1768. doi:10.1080/09652140120089508
- McQueen, A., Tower, S., & Sumner, W. (2011). Interviews with “vapers”: Implications for future research with electronic cigarettes. *Nicotine & Tobacco Research*. doi:10.1093/ntr/ntr088
- McRobbie, H., Whittaker, R., & Bullen, C. (2006). Using nicotine replacement therapy to assist in reducing cigarette consumption before quitting: Another strategy for smoking cessation? *Disease Management and Health Outcomes*, 14, 335–340. doi:10.2165/00115677-200614060-00003
- Mobascher, A., & Winterer, G. (2008). The molecular and cellular neurobiology of nicotine abuse in schizophrenia. *Pharmacopsychiatry*, 41(Suppl. 1), S51–S59. doi:10.1055/s-2008-1081463
- Murray, R. P., Connett, J. E., & Zapawa, L. M. (2009). Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study. *Nicotine & Tobacco Research*, 11, 1076–1082. doi:10.1093/ntr/ntp104
- Myers, C. S., Taylor, R. C., Moolchan, E. T., & Heishman, S. J. (2008). Dose-related enhancement of mood and cognition in smokers administered nicotine nasal spray. *Neuropsychopharmacology*, 33, 588–598. doi:10.1038/sj.npp.1301425
- Nakagawa, Y., Suzuki, T., Ishii, H., Ogata, A., & Nakae, D. (2010). Mitochondrial dysfunction and biotransformation of β -carboline alkaloids, harmine and harmaline, on isolated rat hepatocytes. *Chemico-Biological Interactions*, 188, 393–403. doi:10.1016/j.cbi.2010.09.004
- Nakate, T., Yoshida, H., Ohike, A., Tokunaga, Y., Ibuki, R., & Kawashima, Y. (2003). Comparison of the lung absorption of FK224 inhaled from a pressurized metered dose inhaler and a dry powder inhaler by healthy volunteers. *European Journal of Pharmaceuticals and Biopharmaceutics*, 56, 319–325. doi:10.1016/S0939-6411(03)00113-9
- Newman, S., Anderson, P., Byron, P., Dalby, R., & Peart, J. (2009). *Respiratory drug delivery. Essential theory & practice*. Richmond, VA: Respiratory Drug Delivery Online.
- Next Safety. (2011). *Next Safety products: Nicotine delivery device*. Retrieved from <http://www.webcitation.org/5zIsVmWpU>
- Pankow, J. F. (2001). A consideration of the role of gas/particle partitioning in the deposition of nicotine and other tobacco smoke compounds in the respiratory tract. *Chemical Research in Toxicology*, 14, 1465–1481. doi:10.1021/tx0100901
- Parsons, A. C., Shraim, M., Inglis, J., Aveyard, P., & Hajek, P. (2009). Interventions for preventing weight gain after smoking cessation. *Cochrane Database of Systematic Reviews*, (1). CD006219. doi:10.1002/14651858.CD006219.pub2
- Pettiford, J., Kozink, R. V., Lutz, A. M., Kollins, S. H., Rose, J. E., & McClernon, F. J. (2007). Increases in impulsivity following smoking abstinence are related to baseline nicotine intake and boredom susceptibility. *Addictive Behaviors*, 32, 2351–2357. doi:10.1016/j.addbeh.2007.02.004
- Philip Morris. (2011). *Philip Morris International (PMI) enters into a patent purchase agreement of new technology with the potential to reduce the harm of smoking*. Retrieved from http://www.pmi.com/eng/media_center/press_releases/Pages/201105261249.aspx
- Prigal, S. J., McGavack, T. H., Speer, R. D., & Harris, R. (1947). Aerosol penicillin; blood levels of penicillin obtained by inhalation of aerosols produced by a combined steam generator and aerosolizer, with the use of propylene glycol, tents and a breathing box. *Journal of the American Medical Association*, 134, 932–938.
- Rabinowitz, J. D., Wensley, M., Lloyd, P., Myers, D., Shen, W., Lu, A., et al. (2004). Fast onset medications through thermally generated aerosols. *Journal of Pharmacology and Experimental Therapeutics*, 309, 769–775. doi:10.1124/jpet.103.062893
- Randhawa, K., Mendes, E., & Wanner, A. (2006). Acute effect of cigarette smoke and nicotine on airway blood flow and airflow in healthy smokers. *Lung*, 184, 363–368. doi:10.1007/s00408-006-0006-3
- Rennard, S. I., Glover, E. D., Leischow, S., Daughton, D. M., Glover, P. N., Muramoto, M., et al. (2006). Efficacy of the nicotine inhaler in smoking reduction: A double-blind, randomized trial. *Nicotine & Tobacco Research*, 8, 555–564. doi:10.1080/14622200600789916
- Ritchie, D., Amos, A., & Martin, C. (2010). Public places after smoke-free—a qualitative exploration of the changes in smoking

- behaviour. *Health & Place*, 16, 461–469. doi:10.1016/j.healthplace.2009.12.003
- Rose, J. E. (2006). Nicotine and nonnicotine factors in cigarette addiction. *Psychopharmacology*, 184, 274–285. doi:10.1007/s00213-005-0250-x
- Rose, J. E., & Behm, F. (1987). Refined cigarette smoke as a method for reducing nicotine intake. *Pharmacology Biochemistry and Behavior*, 28, 305–310.
- Rose, J. E., & Behm, F. M. (1991). Psychophysiological interactions between caffeine and nicotine. *Pharmacology Biochemistry and Behavior*, 38, 333–337.
- Rose, J. E., Behm, F. M., & Levin, E. D. (1993). Role of nicotine dose and sensory cues in the regulation of smoke intake. *Pharmacology Biochemistry and Behavior*, 44, 891–900.
- Rose, J. E., Behm, F. M., Westman, E. C., Bates, J. E., & Salley, A. (2003). Pharmacologic and sensorimotor components of satiation in cigarette smoking. *Pharmacology Biochemistry and Behavior*, 76, 243–250. doi:10.1016/j.pbb.2003.07.002
- Rose, J. E., Behm, F. M., Westman, E. C., & Coleman, R. E. (1999). Arterial nicotine kinetics during cigarette smoking and intravenous nicotine administration: Implications for addiction. *Drug and Alcohol Dependence*, 56, 99–107.
- Rose, J. E., Mukhin, A. G., Lokitz, S. J., Turkington, T. G., Herskovic, J., Behm, F. M., et al. (2010). Kinetics of brain nicotine accumulation in dependent and nondependent smokers assessed with PET and cigarettes containing 11C-nicotine. *Proceedings of the National Academy of Sciences of the United States of America*, 107, 5190–5195. doi:10.1073/pnas.0909184107
- Rose, J. E., Rose, S. D., Turner, J. E., & Murugesan, T. (2008). Device and method for delivery of a medicament WO/2008/121610. *World Intellectual Property Organization*. Retrieved from <http://www.wipo.int/pctdb/es/ia.jsp?ia=US2008/058122>
- Rose, J. E., Turner, J. E., Murugesan, T., Behm, F. M., & Laugesen, M. (2010). Pulmonary delivery of nicotine pyruvate: Sensory and pharmacokinetic characteristics. *Experimental and Clinical Psychopharmacology*, 18, 385–394. doi:10.1037/a0020834
- Rose, J. E., Westman, E. C., Behm, F. M., Johnson, M. P., & Goldberg, J. S. (1999). Blockade of smoking satisfaction using the peripheral nicotinic antagonist trimethaphan. *Pharmacology Biochemistry and Behavior*, 62, 165–172.
- Roth, M. T., Andrus, M. R., & Westman, E. C. (2005). Outcomes from an outpatient smoking-cessation clinic. *Pharmacotherapy*, 25, 279–288. doi:10.1592/phco.25.2.279.56957
- Royal College of Physicians. (2007). *Harm reduction in nicotine addiction: Helping people who can't quit*. A report by the Tobacco Advisory Group of Royal College of Physicians, Retrieved from <http://bookshop.rcplondon.ac.uk/details.aspx?e=234>
- Russell, M. A., & Feyerabend, C. (1978). Cigarette smoking: A dependence on high-nicotine boli. *Drug Metabolism Reviews*, 8, 29–57.
- Russell, M. A., Feyerabend, C., & Cole, P. V. (1976). Plasma nicotine levels after cigarette smoking and chewing nicotine gum. *British Medical Journal*, 1, 1043–1046.
- Russell, M. A. H. (1988). Nicotine replacement: The role of nicotine blood levels, their rate of change, and nicotine tolerance. In O. F. Pomerleau & C. S. Pomerleau (Eds.), *Nicotine replacement: A critical evaluation* (pp. 63–94), New York: Alan R. Liss.
- Schneider, N. G., Cortner, C., Gould, J. L., Koury, M. A., & Olmstead, R. E. (2008). Comparison of craving and withdrawal among four combination nicotine treatments. *Human Psychopharmacology*, 23, 513–517. doi:10.1002/hup.947
- Schneider, N. G., Koury, M. A., Cortner, C., Olmstead, R. E., Hartman, N., Kleinman, L., et al. (2006). Preferences among four combination nicotine treatments. *Psychopharmacology*, 187, 476–485. doi:10.1007/s00213-006-0449-5
- Schneider, N. G., Olmstead, R., Nilsson, F., Mody, F. V., Franzon, M., & Doan, K. (1996). Efficacy of a nicotine inhaler in smoking cessation: A double-blind, placebo-controlled trial. *Addiction*, 91, 1293–1306.
- Schneider, N. G., Olmstead, R. E., Franzon, M. A., & Lunell, E. (2001). The nicotine inhaler clinical pharmacokinetics and comparison with other nicotine treatments. *Clinical Pharmacokinetics*, 40, 661–684. doi:10.2165/00003088-200140090-00003
- Schneider, N. G., Olmstead, R. E., Nides, M., Mody, F. V., Otte-Colquette, P., Doan, K., et al. (2004). Comparative testing of 5 nicotine systems: Initial use and preferences. *American Journal of Health Behavior*, 28, 72–86. Retrieved from <http://www.ajhb.org/index.htm>. doi:10.5993/AJHB.28.1.8
- Schuh, K. J., Schuh, L. M., Henningfield, J. E., & Stitzer, M. L. (1997). Nicotine nasal spray and vapor inhaler: Abuse liability assessment. *Psychopharmacology*, 130, 352–361.
- Schuster, J., Rubsamen, R., Lloyd, P., & Lloyd, J. (1997). The AERX aerosol delivery system. *Pharmaceutical Research*, 14, 354–357.
- Sellick, H., & Widdicombe, J. G. (1971). Stimulation of lung irritant receptors by cigarette smoke, carbon dust, and histamine aerosol. *Journal of Applied Physiology*, 31, 15–19.
- Shen, X., Hindle, M., & Byron, P. R. (2004). Effect of energy on propylene glycol aerosols using the capillary aerosol generator. *International Journal of Pharmaceutics*, 275, 249–258. doi:10.1016/j.ijpharm.2004.02.005
- Shiffman, S., Hughes, J. R., Pillitteri, J. L., & Burton, S. L. (2003). Persistent use of nicotine replacement therapy: An analysis of actual purchase patterns in a population based sample. *Tobacco Control*, 12, 310–316. doi:10.1136/tc.12.3.310
- Silagy, C., Lancaster, T., Stead, L., Mant, D., & Fowler, G. (2004). Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews*, (3). doi:10.1002/14651858.CD000146.pub3
- Stapleton, J. A., Russell, M. A. H., Sutherland, G., & Feyerabend, C. (1998). Nicotine availability from Eclipse tobacco-heating cigarette. *Psychopharmacology*, 139, 288–290.

- Stead, L. F., Perera, R., Bullen, C., Mant, D., & Lancaster, T. (2008). Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews*, (4). doi:10.1002/14651858.CD000146.pub3
- Sumner, W. (2006). Permissive nicotine regulation as a complement to traditional tobacco control. *BMC Public Health*, 5, 1–9. doi:10.1186/1471-2458-5-18
- Sumner, W., II. (2003). Estimating the health consequences of replacing cigarettes with nicotine inhalers. *Tobacco Control*, 12, 124–132. doi:10.1136/tc.12.2.124
- Sweanor, D. (2000). Regulatory imbalance between medicinal and non-medicinal nicotine. *Addiction*, 95(Suppl. 1), S25–S28. doi:10.1080/09652140032044
- Sweanor, D. T. (1999). Policy options to reduce tobacco-caused mortality. *Journal of Addictive Diseases*, 18, 1–11.
- Teague, C. E. J. (1983). *Implications and activities arising from correlation of smoke pH with nicotine impact, other smoke qualities, and cigarette sales*. Retrieved from <http://legacy.library.ucsf.edu/tid/rte53d00/pdf>
- Thomson, G., Wilson, N., Blakely, T., & Edwards, R. (2010). Ending appreciable tobacco use in a nation: Using a sinking lid on supply. *Tobacco Control*, 19, 431–435. doi:10.1136/tc.2010.036681
- Timmons, R. D., Simis, K. S., Lei, M., Lu, A. T., Sharma, K., Hale, R. L., et al. (2008). Feasibility study of nicotine aerosol generation using the Staccato system. *Respiratory Drug Delivery Europe*, 2, 359–364. Retrieved from <http://www.rddonline.com>
- Tobin, M. J., & Sackner, M. A. (1982). Monitoring smoking patterns of low and high tar cigarettes with inductive plethysmography. *American Review of Respiratory Disease*, 126, 258–264.
- Tonnesen, P., & Mikkelsen, K. L. (2000). Smoking cessation with four nicotine replacement regimes in a lung clinic. *European Respiratory Journal*, 16, 717–722. doi:10.1034/j.1399-3003.2000.16d25.x
- Tonnesen, P., Norregaard, J., Mikkelsen, K., Jorgensen, S., & Nilsson, F. (1993). A double-blind trial of a nicotine inhaler for smoking cessation. *Journal of the American Medical Association*, 269, 1268–1271.
- Trehy, M. L., Ye, W., Hadwiger, M. E., Moore, T. W., Allgire, J. F., Woodruff, J. T., et al. (2011). Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. *Journal of Liquid Chromatography & Related Technologies*, 34, 1442–1458. Retrieved from <http://dx.doi.org/10.1080/10826076.2011.572213>
- Vagg, R., & Chapman, S. (2005). Nicotine analogues: A review of tobacco industry research interests. *Addiction*, 100, 701–712. doi:10.1111/j.1360-0443.2005.01014.x
- Vinegar, A., Jepson, G. W., Cisneros, M., Rubenstein, R., & Brock, W. J. (2000). Setting safe acute exposure limits for halon replacement chemicals using physiologically based pharmacokinetic modeling. *Inhalation Toxicology*, 12, 751–763. doi:10.1080/08958370050085174
- Volkow, N. D., Fowler, J. S., & Wang, G. J. (2002). Role of dopamine in drug reinforcement and addiction in humans: Results from imaging studies. *Behavioural Pharmacology*, 13, 355–366. doi:10.1097/00008877-200209000-00008
- Warner, K. E., Slade, J., & Sweanor, D. T. (1997). The emerging market for long-term nicotine maintenance. *Journal of the American Medical Association*, 278, 1087–1092.
- Watkins, S. S., Koob, G. F., & Markou, A. (2000). Neural mechanisms underlying nicotine addiction: Acute positive reinforcement and withdrawal. *Nicotine & Tobacco Research*, 2, 19–37. doi:10.1080/14622200050011277
- Wayne, G. F., & Connolly, G. N. (2004). Application, function, and effects of menthol in cigarettes: A survey of tobacco industry documents. *Nicotine & Tobacco Research*, 6(Suppl. 1), S43–S54. doi:10.1080/14622203310001649513
- West, R. (1992). The ‘nicotine replacement paradox’ in smoking cessation: How does nicotine gum really work? *British Journal of Addiction*, 87, 165–167.
- West, R., Hajek, P., Foulds, J., Nilsson, F., May, S., & Meadows, A. (2000). A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology*, 149, 198–202. doi:10.1007/s002130000382
- West, R., Hajek, P., Nilsson, F., Foulds, J., May, S., & Meadows, A. (2001). Individual differences in preferences for and responses to four nicotine replacement products. *Psychopharmacology*, 153, 225–230. doi:10.1007/s002130000577
- Westenberger, B. J. (2009). *Evaluation of e-cigarettes*. (DPATRFY-09-23). United States Food & Drug Administration. Retrieved from <http://www.fda.gov/downloads/Drugs/ScienceResearch/UCM173250.pdf>
- Widdicombe, J. (2009). Lung afferent activity: Implications for respiratory sensation. *Respiratory Physiology & Neurobiology*, 167, 2–8. doi:10.1016/j.resp.2008.09.012
- Wu, P., Wilson, K., Dimoulas, P., & Mills, E. J. (2006). Effectiveness of smoking cessation therapies: A systematic review and meta-analysis. *BMC Public Health*, 6, 300. doi:10.1186/1471-2458-6-300