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Addictive Behaviors



Tobacco harm reduction: The need for new products that can compete with cigarettes



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HIGHLIGHTS

- Tobacco harm reduction aims to reduce illness and death caused by smoking tobacco.
- The medical and regulatory consensus is that nicotine itself is relatively safe.
- Snus use in Sweden provides strong evidence in support of harm reduction.
- E-cigarettes are seen by many smokers as an attractive alternative to cigarettes.
- Regulated, safer nicotine alternatives may substantially improve public health.

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ABSTRACT

Over the last 50 years, the concept of tobacco harm reduction has been well established. It is now understood that nicotine itself is not very harmful and nicotine replacement therapy products have been widely used as an aid to quit, reduce to quit or temporarily abstain from smoking for many years. The popularity of the unlicensed electronic cigarette has increased despite an unknown risk profile and snus use in Sweden provides strong evidence in support of a harm reduction strategy. The regulatory environment around harm reduction has changed in the UK and is continuing to evolve across the globe. The need for more appealing, licensed nicotine products capable of competing with cigarettes sensorially, pharmacologically and behaviourally is considered by many to be the way forward. The significant positive impact on public health that could be gained from encouraging people to switch from cigarettes to licensed medicinal nicotine products cannot be ignored.

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1. Harm reduction: history and current perspectives

The concept of tobacco harm reduction is well established. In 1976, Professor Michael Russell wrote: “People smoke for nicotine but they die from the tar”, and suggested that the ratio of tar to nicotine could be the key to safer smoking, specifically a low-tar, medium-nicotine cigarette (Russell, 1976). Despite innovations in the mid-1970s, several filtered products delivered as much tar and nicotine as the original, unfiltered brands (Kozłowski & O’Connor, 2002). As understanding improved, new research in 1982 confirmed that smokers inhaled less smoke from a nicotine-enriched cigarette than a control cigarette, equal in all aspects besides nicotine yield (Fagerström, 1982).

Since the White Paper, ‘Smoking Kills’, was published in 1998 (Department of Health, 1998), a variety of tobacco-control policies to reduce smoke prevalence have been implemented in the UK, and around the world (Royal College of Physicians, 2007). The National Institute for Health and Care Excellence (NICE) defined tobacco harm reduction as “reducing the illnesses and deaths caused by smoking tobacco – among people who smoke and those around them” (NICE, 2011). In parallel, medical opinion has evolved, recognizing the potential health benefit of smokers shifting from cigarettes to pharmaceutically-regulated nicotine products. In fact, in the last decade, the medical community has urged regulators to consider harm reduction strategies to reduce rates of smoking (NICE, 2011; Royal College of Physicians, 2007, 2012). Similarly, in the USA, the Family Smoking Prevention and Tobacco Control Act of 2009 aims to significantly reduce harm and the risk of tobacco-related disease to individual tobacco users (FDA, 2009).

Although medicinal nicotine products were initially regulated as prescription only, they have been available over the counter (OTC) as a General Sales List product for a decade in many countries. Further restrictions on the use of nicotine replacement therapy (NRT) in specific populations, such as pregnant women, those with heart disease, diabetes, liver or kidney problems, and children aged 12–18 years, have gradually been minimized (MHRA, 2005), and the indication for NRT extended to include ‘cut down to quit’ and ‘temporary abstinence’, along with cessation (MHRA, 2010a). Most regulators, therefore, apply no time limit for NRT use to support reduction, confident that this alone facilitates quitting and may have direct health benefits, not least

to those living with the smoker. Similarly, many countries also support ‘temporary abstinence’ (Gartner, Hall, & McNeill, 2010). An overview of approaches over time in the UK is presented in Fig. 1.

In 2009, the UK Medicines and Healthcare products Regulatory Agency (MHRA) approved an extension to include harm reduction as an indication for the Nicorette® Inhalator (McNeil AB, Helsingborg, Sweden) (MHRA, 2009). Resulting from the review of its approach to smoking cessation in 2010, it advocated an indication for harm reduction for all licensed nicotine-containing products (MHRA, 2010b).

The recently updated public health strategy in the UK recognizes that many smokers may not want, or be able, to quit smoking, but would like a safer alternative to cigarettes (HM Government, 2011). NICE guidelines in the UK published in June 2013 recommend medicinal nicotine use on a long-term basis when needed to help people stop, cut down prior to quitting, reduce their level of, or temporarily abstain from, smoking. These guidelines cover the use of licensed nicotine-containing products, and those that might be licensed by the MHRA in the future such as those electronic cigarettes (e-cigarettes) demonstrating the necessary quality and safety standards (NICE, 2013).

In other countries, a harm reduction strategy is supported by an increasing number of experts. While NRT is only licensed in this way in the UK, the long-standing Swedish policy of accepting moist snuff (snus) to compete with burnt tobacco has provided evidence of significant health benefits; male smoking and tobacco-related mortality in Sweden are among the lowest in the world (Rodu, Stegmayr, Nasic, & Asplund, 2002). There is also evidence suggesting that snus uptake can result in moving from high- to low-risk tobacco use or quitting altogether (Ramström, 2011). This indicates the benefits that might conservatively be expected if NRT was more widely licensed for harm reduction.

2. Safety of nicotine as an alternative to smoked tobacco

It is generally understood that it is not nicotine itself that is harmful, but the method of delivery, i.e. burning tobacco (ASH, 2007). Moreover, it has been proposed that a switch of only 1% of smokers a year from smoking to less harmful nicotine sources could potentially save around 60 000 lives in 10 years in the UK alone (Lewis, Arnott, Godfrey, & Britton, 2005).

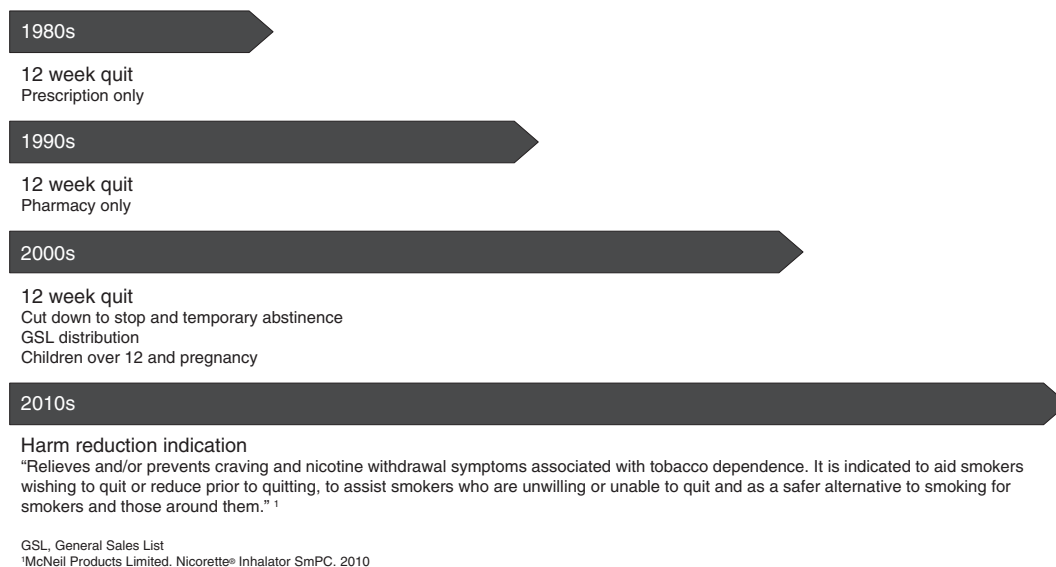


Fig. 1. Nicotine replacement therapy regulation in the UK over the last 30 years.

2.1. Nicotine and cancer

Even with snus, which is not pharmaceutical-grade nicotine but a refined tobacco still containing nitrosamines and heavy metals, the causal association with cancer is weak. Observations from long-term snus use show little evidence, or inconsistent results, of increased cancer risk compared with non-tobacco users (Lewin et al., 1998; Luo et al., 2007; Schildt, Eriksson, Hardell, & Magnuson, 1998). Furthermore, a recent meta-analysis found no association between snus and cancer of the oropharynx, esophagus, stomach, pancreas, lung or other sites (Lee, 2011).

For methodological and ethical reasons, little research has been done on the long-term health effects (including cancer) of nicotine in humans. However, the only large, long-term study published to date (The Lung Health Study) found no link between NRT and cancer among former smokers (Murray, Connert, & Zapawa, 2009).

This has led both the UK MHRA and the Royal College of Physicians to conclude that there is no evidence that medicinal nicotine causes cancer (MHRA, 2010c; Royal College of Physicians, 2007). While many components in tobacco smoke have been determined to be carcinogens, authoritative bodies do not include nicotine in this list, including the International Agency for Research on Cancer (International Agency for Research on Cancer, 2007), the US Surgeon General (US Department of Health & Human Services, 2010) and the US Food and Drug Administration (FDA) (FDA, 2012).

2.2. Nicotine and cardiovascular disease

Although it is recognized that medicinal nicotine causes temporary changes to the cardiovascular system during use (e.g. increased blood pressure and elevated heart rate), these changes are transient (Benowitz, Hansson, & Jacob, 2002). Furthermore, epidemiology studies have not found NRT use to be linked to the development of cardiovascular disease (CVD) (Greenland, Satterfield, & Lanes, 1998; Hubbard et al., 2005; Kimmel et al., 2001; Murray et al., 1996) and studies have shown that NRT need not be contraindicated for smokers with CVD (Hubbard et al., 2005; Joseph et al., 1996; McRobbie & Hajek, 2001). Several studies have evaluated CVD risk in long-term users of snus; a recent meta-analysis of eight prospective, observational studies concluded that snus use was not associated with acute myocardial infarction (Hansson et al., 2012).

The UK Royal College of Physicians states that NRT does not increase the incidence of acute cardiovascular events or of sudden death in healthy volunteers, the general population or in patients with pre-existing CVD (Royal College of Physicians, 2007). Further the FDA does not consider nicotine to be a significant cardiovascular toxicant (FDA, 2012).

3. Current alternative nicotine products

3.1. Nicotine replacement therapy

NRT is the term given to products containing medicinal nicotine that have met regulatory authority standards for quality, safety and efficacy.

Table 1

Nicotine replacement therapies available in the UK.
Information obtained from the British National Formulary.

Type	Available doses
Nicotine transdermal patches	Worn over 16 h: 5, 10, 15 and 25 mg Worn over 24 h: 7, 14, 20, 21 and 30 mg
Nicotine chewing gum	2 and 4 mg
Nicotine sublingual tablet	2 mg
Nicotine lozenge	1, 1.5, 2 and 4 mg
Nicotine inhalation cartridge plus mouthpiece	Cartridge containing 15 mg
Nicotine metered nasal spray	0.5 mg per spray
Nicotine oral spray	1 mg per spray

NRTs (patches, gums, lozenges, microtabs, sprays and inhalators) have been studied extensively for over 30 years in helping smokers quit, reduce to quit or temporarily abstain from smoking. Table 1 shows the NRTs currently available in the UK.

NRT increases the rate of quitting by 50–70% when compared with placebo or no treatment (Stead et al., 2012). However, on a population level, the impact of NRT in absolute terms is modest. The proportion of smokers considering making a quit attempt at any point is small, and of those using NRT without any formal behavioral support, just 7–10% remain cigarette-free at 52 weeks (Stead, Perera, Bullen, Mant, & Lancaster, 2008).

Although conventional NRTs do not adequately replicate the act of cigarette smoking, the recent surge in the popularity of e-cigarettes seems to be due in part to this very fact. Furthermore, there is growing interest in the development of consumer-acceptable inhaled nicotine delivery systems with absorption kinetics similar to typical cigarettes as a harm reduction technique (Benowitz, 2008; Caldwell, Sumner, & Crane, 2012).

3.2. E-cigarettes

Historically, e-cigarettes have been outside of the medicines licensing regime, with no independent oversight of quality, safety or efficacy. However, as a result of the recent MHRA announcement to regulate all nicotine-containing products as medicines, e-cigarettes will require a medicine license in the UK from 2016. This should allow time for manufacturers to ensure that their products meet the required medicines' quality standard.

Several studies have reported e-cigarette use to aid smoking reduction or temporary abstinence (Caponnetto, Polosa, Russo, Leotta, & Campagna, 2011; Polosa et al., 2011; Siegel, Tanwar, & Wood, 2011), and as a quitting aid (Caponnetto et al., 2011; Siegel et al., 2011). Another study has described their use to reduce nicotine craving, with a significant difference in craving levels reported with e-cigarettes than placebo (Bullen et al., 2010).

There is, however, far less evidence regarding safety and quality of e-cigarettes. Recent studies found that levels of nicotine (Goniewicz, Kuma, Gawron, Knysak, & Kosmider, 2013) and nicotine-related impurities (Trehy et al., 2011) varied considerably across brands. Nicotine content was inaccurately labeled by some manufacturers (Trehy et al., 2011) and there is the possibility that metals, or chemicals from plastics in the delivery device, may leach into the vapor before inhalation (Williams, Villarreal, Bozhilov, Lin, & Talbot, 2013).

When smokers were asked to give their reasons for using e-cigarettes, the most popular answers included a perception that they are less harmful than tobacco, as a substitute for smoking where smoking is not allowed, to quit or avoid relapse, to deal with tobacco craving or tobacco-withdrawal symptoms and because they are cheaper than smoking (ASH, 2012; Etter & Bullen, 2011).

4. Limitations of existing NRTs

Currently available forms of NRT may fail to help many smokers quit because they do not deliver nicotine in the same way as cigarettes (Schneider, Lunell, Olmstead, & Fagerström, 1996; Schneider, Olmstead, Franzon, & Lunell, 2001). However, smoking is a conditioned habit that is triggered by various environmental cues, and smokers enjoy the many rituals associated with smoking (Fagerström, 2012). Most current NRTs do not replace these unique sensory cues or rituals (Fagerström, 2012; Rose, 2006), making it difficult to convince habitual smokers to switch to them or to continue use once tried. After all, cigarette smokers long for a cigarette, not nicotine, much like hunger is directed to food, not carbohydrate.

The need for more appealing licensed nicotine products capable of competing with cigarettes, and meeting smokers where they are rather than beseeching them yet again to change, is considered by many to be

the way forward. There are no circumstances when it is safer to smoke than to use medicinal nicotine (MHRA, 2005) and a lifetime use of NRT will be considerably less harmful than smoking (NICE, 2013). UK smoking prevalence has plateaued in recent years to around 20% (Office for National Statistics, 2011), with a similar picture seen across other western countries (European Commission, 2012). Smokers know the risks, but find quitting difficult for a variety of reasons. New medicinal nicotine products better replicating the smoking experience have the potential to radically reduce both individual risk and public smoking-related morbidity and mortality.

5. Future challenges in harm reduction

The regulatory environment around harm reduction has changed in the UK and continues to evolve across the globe. An important debate persists, with reasonable concerns that must be considered. The MHRA's endorsement of harm reduction may seem logical given the alternative, though there are risks that have to be managed, particularly as products that look and feel more like a cigarette reach the market.

One example is the perception that medicinal nicotine could act as a gateway to smoking tobacco, establishing a dependence on nicotine in non-smokers, although several studies have challenged this. The data analyzed indicate that those who start using smokeless tobacco are less likely to smoke cigarettes (Rodu & Cole, 2010), and the odds of initiating daily smoking are significantly lower for men who start using snus than for those who do not (Ramström & Foulds, 2006). Although e-cigarettes may have a similar impact as snus, with regard to the gateway hypothesis, further research is needed. A recent study in the UK found that <1% of adults who had never smoked reported having tried e-cigarettes (ASH, 2012). Similarly, an online study of 2649 adults in the USA reported e-cigarette use in 0.8% of non-smokers (Pearson, Richardson, Niaura, Vallone, & Abrams, 2012).

Nevertheless, the unintended consequences of advocating e-cigarettes, particularly in adolescents, should be considered in future research as their use increases. A recent survey among middle and high-school students in the US showed that e-cigarette use had doubled in the space of a year; ever e-cigarette use increased from 3.3% to 6.8%; current e-cigarette use increased from 1.1% to 2.1%; and current use of both conventional and e-cigarettes increased from 0.8% to 1.6% from 2011 to 2012 (Corey et al., 2013). However, it appears that current e-cigarette use in children is largely confined to those who have already tried smoking. One recent survey commissioned by Action on Smoking and Health in the UK report that among 16–18-year-olds who have never smoked, only 1% have tried e-cigarettes once or twice (ASH, 2013).

It is possible that adolescents with co-morbidities or behavioral problems seeking relief from their symptoms by use of nicotine may be more likely to turn to e-cigarettes as they become widespread. This, of itself, may not be a bad thing, provided that e-cigarettes are being used as an alternative by adolescents who would otherwise have smoked, and that it does not lead to 'gateway' among those who would not.

Until now there was the concern that unregulated e-cigarettes claiming health benefit over cigarettes could cause negative effects currently not seen with cigarettes. Medicinal nicotine, licensed as NRT, undergoes careful quantitative and qualitative analysis of its composition at key points throughout its shelf-life. This enables manufacturers, regulators and consumers to be confident of its quality and safety. Although e-cigarettes are currently not subjected to the same testing and regulatory authority data review, the requirement for a medicines license from 2016 should negate these concerns in the future. Until that time, while likely to be safer than cigarettes, evidence of safety relating to medicinal nicotine, gained over >30 years' marketed experience and laboratory testing, cannot be extrapolated to apply to them in equal measure.

It was envisaged, based on the draft European Tobacco Product Directive, that a similar policy towards the licensing of e-cigarettes would be adopted across the EU, although this is unlikely now. While this could provide the assurances that consumers should expect regarding safety and quality, and support the advertising of these products in a responsible way, there are some concerns that need to be addressed. Unfortunately, the level of market access for medicinal OTC products varies by country, even in the EU. In the UK, NRT available on the General Sales List can compete effectively with tobacco at the point of sale without pharmacist or other healthcare professional oversight. In many other EU countries, these products must be sold in pharmacies, often only displayed 'behind the counter'. Individual EU Governments can remedy this within the existing medicines legislation, and must do so for medicines regulation to offer a compelling regulatory framework for e-cigarettes across the region.

There seems to be some agreement, however, that the popularity of e-cigarettes is because they more closely address the smokers' needs than currently available NRTs. Therefore, licensed, medicinal nicotine-containing products are required that can demonstrate a safety profile similar to other NRT products, but that also satisfy smokers' needs for rapid nicotine delivery and the smoking ritual.

Following the harm reduction indication for NRT in the UK, the tobacco industry has started to invest in products that can meet medicines legislation quality standards (British American Tobacco, 2011). These corporations are committed to meeting the needs of smokers, which of course includes finding safer but equally satisfying alternatives to cigarettes. They will not want their products to be over-medicalized as smokers do not see themselves as ill, and so do not seek a medicine. However, some companies are demonstrating that they are prepared to work within a regulatory framework focusing on medicines' standard quality and safety, allowing appropriate oversight of communication through advertising to smokers. If the model proposed by the MHRA receives wider acceptance, we believe that the tobacco industry could actually become part of the solution to cigarette smoking, investing their resources in a more targeted way towards finding satisfying alternatives for those who do not wish, or are unable, to eliminate nicotine from their lives.

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Contributors

Karl Fagerström and Kevin Bridgman defined the scope of the manuscript, reviewed the content critically at all stages and read and approved the final version for publication.

Conflicts of interest

Karl Olov Fagerström is a consultant to a number of companies (Pfizer, Nicovium, Novartis, Nicoventures, Independent Pharmaceutica, Moberg Pharma, Chrono) with an interest in treatments for tobacco dependence.

Kevin Bridgman is an employee of Nicoventures Limited.

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References

- ASH (Action on Smoking, Health) (2007). *Nicotine replacement therapy guidelines for healthcare professionals on using nicotine replacement therapy for smokers not yet ready to stop smoking*. (17 pp.).
- ASH (Action on Smoking, Health) (2012). *E-cigarette use in Great Britain: 2010 and 2012*. (5 pp.).
- ASH (Action on Smoking, Health) (2013). *Use of e-cigarettes in Great Britain among adults and young people*. (4 pp.).

- Benowitz, N. L. (2008). Clinical pharmacology of nicotine: Implications for understanding, preventing, and treating tobacco addiction. *Clinical Pharmacology & Therapeutics*, 83, 531–541.
- Benowitz, N. L., Hansson, A., & Jacob, P. I. (2002). Cardiovascular effects of nasal and transdermal nicotine and cigarette smoking. *Hypertension*, 39, 1107–1112.
- British American Tobacco (2011). British American Tobacco establishes stand-alone company, Nicoventures Limited. News release. Available at: http://www.bat.com/group/sites/uk_3mnfen.nsf/vwPagesWebLive/DO8FLL93?opendocument&SKN=1
- 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.
- Caldwell, B., Sumner, W., & Crane, J. (2012). A systematic review of nicotine by inhalation: Is there a role for the inhaled route? *Nicotine & Tobacco Research*, 14, 1127–1139.
- Caponnetto, P., Polosa, R., Russo, C., Leotta, C., & Campagna, D. (2011). Successful smoking cessation with electronic cigarettes in smokers with a documented history of recurring relapses: A case series. *Journal of Medical Case Reports*, 5, 585.
- Corey, C., Wang, B., Johnson, S. E., Apelberg, B., Husten, C., et al. (2013). Notes from the field: Electronic cigarette use among middle and high school students – United States, 2011–2012. *Morbidity and Mortality Weekly Report*, 62, 729–730.
- Department of Health (1998). *Smoking kills: A white paper on tobacco*.
- Etter, J.-F., & Bullen, C. (2011). Electronic cigarette: Users profile, utilization, satisfaction and perceived efficacy. *Addiction*, 106, 2017–2028.
- European Commission (2012). *Attitudes of Europeans towards tobacco: Special Eurobarometer 385*. (167 pp.).
- Fagerström, K. O. (1982). Effects of a nicotine-enriched cigarette on nicotine titration, daily cigarette consumption, and levels of carbon monoxide, cotinine, and nicotine. *Psychopharmacology*, 77, 164–167.
- Fagerström, K. O. (2012). Determinants of tobacco use and renaming the FTND to the Fagerstrom Test for Cigarette Dependence. *Nicotine & Tobacco Research*, 14, 75–78.
- FDA (Food, Drug Administration) (2009). Family Smoking Prevention and Tobacco Control Act. Available at: <http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm298595.htm>
- FDA (Food, Drug Administration) (2012). Harmful and potentially harmful constituents in tobacco products and tobacco smoke: established list. *Federal Register*, 77, 20034–20037.
- Gartner, C., Hall, W., & McNeill, A. (2010). Harm reduction policies for tobacco. In T. Rhodes, & D. Hedrich (Eds.), *Harm reduction: Evidence, impacts and challenges* (pp. 255–273). Europa: EMCDA.
- Goniewicz, M. L., Kuma, T., Gawron, M., Knysak, J., & Kosmider, L. (2013). Nicotine levels in electronic cigarettes. *Nicotine & Tobacco Research*, 15, 158–166.
- Greenland, S., Satterfield, M. H., & Lanes, S. F. (1998). A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Safety*, 18, 297–308.
- Hansson, J., Galanti, M. R., Hergens, M.-P., Fredlund, P., Ahlbom, A., et al. (2012). Use of snus and acute myocardial infarction: Pooled analysis of eight prospective observational studies. *European Journal of Epidemiology*, 27, 771–779.
- HM Government (2011). *Healthy lives, healthy people: A tobacco control plan for England*. (57 pp.).
- Hubbard, R., Lewis, S., Smith, C., Godfrey, C., Smeeth, L., et al. (2005). Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. *Tobacco Control*, 14, 416–421.
- International Agency for Research on Cancer (2007). Some tobacco-specific N-nitrosamines. *IACR Monograph*, 89 (583 pp.).
- Joseph, A., Norman, S., Ferry, L., Prochazka, A. V., Westman, E. C., et al. (1996). The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *New England Journal of Medicine*, 335, 1792–1798.
- Kimmel, S. E., Berlin, J. A., Miles, C., Jaskowiak, J., Carson, J. L., & Strom, B. L. (2001). Risk of acute first myocardial infarction and use of nicotine patches in a general population. *Journal of the American College of Cardiology*, 37, 1297–1302.
- Kozlowski, L. T., & O'Connor, R. J. (2002). Cigarette filter ventilation is a defective design because of misleading taste, bigger puffs, and blocked vents. *Tobacco Control*, 11(Suppl. 1), I40–I50.
- Lee, P. N. (2011). Summary of the epidemiological evidence relating snus to health. *Regulatory Toxicology and Pharmacology*, 59, 197–214.
- Lewin, F., Norell, S. E., Johansson, H., Gustavsson, P., Wennerberg, J., et al. (1998). Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck: A population-based case-referent study in Sweden. *Cancer*, 82, 1367–1375.
- Lewis, S., Arnott, D., Godfrey, C., & Britton, J. (2005). Public health measures to reduce smoking prevalence in the UK: How many lives could be saved? *Tobacco Control*, 14, 251–254.
- Luo, J., Ye, W., Zendehdel, K., Adami, J., Adami, H. O., et al. (2007). Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: A retrospective cohort study. *Lancet*, 369, 2015–2020.
- McRobbie, H., & Hajek, P. (2001). Nicotine replacement therapy in patients with cardiovascular disease: Guidelines for health professionals. *Addiction*, 96, 1547–1551.
- MHRA (Medicines, Healthcare products Regulatory Agency) (2005). *Report of the Committee on Safety of Medicines Working Group on nicotine replacement therapy*.
- MHRA (Medicines, Healthcare products Regulatory Agency) (2009, December). *Public assessment report*. The use of nicotine replacement therapy to reduce harm in smokers (9 pp.).
- MHRA (Medicines, Healthcare products Regulatory Agency) (2010a). *Drug safety update*. (8 pp.).
- MHRA (Medicines, Healthcare products Regulatory Agency) (2010b). *Consultation letter MLX 364: The regulation of nicotine containing products*. (28 pp.).
- MHRA (Medicines, Healthcare products Regulatory Agency) (2010c). *MHRA public assessment report*. The use of nicotine replacement therapy to reduce harm in smokers (9 pp.).
- Murray, R. P., Bailey, W. C., Daniels, K., Bjornson, W. M., Kurnow, K., et al. (1996). Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. *Chest*, 109, 438–445.
- 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.
- NICE (National Institute for Health and Care Excellence) (2011). *Public health guidance scope: Tobacco: Harm-reduction approaches to smoking*. (London).
- NICE (National Institute for Health and Care Excellence) (2013). *Public Health Guideline 45. Tobacco: Harm-reduction approaches to smoking* (London).
- Office for National Statistics (2011). *General lifestyle survey overview*. (10 pp.).
- Pearson, J. L., Richardson, A., Niaura, R. S., Vallone, D.M., & Abrams, D. B. (2012). E-cigarette awareness, use, and harm perceptions in US adults. *American Journal of Public Health*, 102, 1758–1766.
- Polosa, R., Caponnetto, P., Morjaria, J. B., Papale, G., Campagna, D., & Russo, C. (2011). Effect of an electronic nicotine delivery device (e-cigarette) on smoking reduction and cessation: A prospective 6-month pilot study. *BMC Public Health*, 11, 786.
- Ramström, L. (2011). Commentary on Lund et al. (2011): Consolidating the evidence on effectiveness of snus for smoking cessation – Implications for public health. *Addiction*, 106, 168–169.
- Ramström, L. M., & Foulds, J. (2006). Role of snus in initiation and cessation of tobacco smoking in Sweden. *Tobacco Control*, 15, 210–214.
- Rodu, B., & Cole, P. (2010). Evidence against a gateway from smokeless tobacco use to smoking. *Nicotine & Tobacco Research*, 12, 530–534.
- Rodu, B., Stegmayr, B., Nasic, S., & Asplund, K. (2002). Impact of smokeless tobacco use on smoking in northern Sweden. *Journal of Internal Medicine*, 252, 398–404.
- Rose, J. E. (2006). Nicotine and nonnicotine factors in cigarette addiction. *Psychopharmacology (Berlin)*, 184, 274–285.
- Royal College of Physicians (2007). Harm reduction in nicotine addiction: Helping people who can't quit. *A report by the Tobacco Advisory Group of the Royal College of Physicians*.
- Royal College of Physicians (2012). Fifty years since smoking and health. Progress, lessons and priorities for a smoke-free UK. In J. Britton (Ed.), *Report of conference proceedings*. London: RCP (64 pp.).
- Russell, M.A. (1976). Low-tar medium-nicotine cigarettes: A new approach to safer smoking. *British Medical Journal*, 1, 1430–1433.
- Schildt, E. B., Eriksson, M., Hardell, L., & Magnuson, A. (1998). Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. *International Journal of Cancer*, 77, 341–346.
- Schneider, N., Lunell, E., Olmstead, R. E., & Fagerström, K. O. (1996). Clinical pharmacokinetics of nasal nicotine delivery. A review and comparison to other nicotine systems. *Clinical Pharmacokinetics*, 31, 65–80.
- 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.
- Siegel, M. B., Tanwar, K. L., & Wood, K. S. (2011). Electronic cigarettes as a smoking-cessation: Tool results from an online survey. *American Journal of Preventive Medicine*, 40, 472–475.
- Stead, L. F., Perera, R., Bullen, C., Mant, D., & Hartmann-Boyce, J. (2012). Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews*, 11, CD000146.
- Stead, L. F., Perera, R., Bullen, C., Mant, D., & Lancaster, T. (2008). Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews*, 1, CD000146.
- Treth, 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.
- US Department of Health and Human Services (2010). How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease. *A report of the Surgeon General* (19 pp.).
- Williams, M., Villarreal, A., Bozhilov, K., Lin, S., & Talbot, P. (2013). Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS One*, 8, e57987.