ARTICLE

Why is it so hard to quit smoking?

Lynne Dawkins explores the role of nicotine and non-nicotine contributions to smoking and considers a promising new device for kicking the habit

Smoking is the single most preventable major cause of illness and early death, with nearly one in five deaths (in those aged 35 or above) caused by smoking. Smoking has a multitude of effects on health, that most smokers are aware of. So why do more than one in five adults continue to smoke? And why is it so hard to give up?

In England cigarette smoking is responsible for an estimated 81,700 deaths per year, in other words, 223 people a day – or nine people an hour – die from their smoking 'habit'. An estimated 36 per cent of all respiratory disease deaths, 29 per cent of cancer deaths and 14 per cent of all circulatory disease deaths are attributable to smoking. This figure rises to 87 per cent of deaths from chronic obstructive lung disease and 82 per cent of deaths from lung, bronchus and trachea cancer (NHS Information Centre: tinyurl.com/cym3apk).

On an individual level, a long-term regular smoker loses an average of 10 years of their life (Doll et al., 2004). That is, approximately 8 out of 10 non-smokers live beyond 70 years compared to only half of long-term smokers (Kenny, 2012). If it doesn't kill you, smoking has multiple other ways of making your life a misery: it increases the risk of stroke, angina, emphysema, high blood pressure, thrombosis, asthma, cataracts, ulcers, erectile dysfunction and many more (tinyurl.com/74jlw). Given that most smokers are aware of these harmful effects, why do 21 per cent of the adult population continue to smoke? (NHS Information Centre: tinyurl.com/cym3apk). And why are more than 95–97 per cent of unaided quit attempts unsuccessful (Hughes et al., 2004)?

The problem with nicotine

Whilst tobacco smoke contains thousands of chemicals, it is the nicotine content that is generally thought to keep people hooked. Smoking is an extremely effective way of delivering nicotine to the brain. It is rapidly absorbed through the lungs into the bloodstream, where it is carried directly to the heart and reaches the brain in about 6–10 seconds (akin to an intravenous injection: Rose et al., 2000). Because of this direct route, nicotine does not get a chance to dissipate, so the high concentration of nicotine in the lungs from a puff on a cigarette remains in the blood as this 'hit' (often referred to as a 'bolus') until it reaches the brain. Whilst addictive, nicotine is relatively safe; it's the carbon monoxide (CO; which prevents oxygen transportation around the body) and tar (which deposits in the lungs and airways and contains carcinogens) that carry the health risks of smoking.

The brain has its own receptors for nicotine – so-called 'nicotinic acetylcholine' receptors. Many of these are located on the cell bodies in the ventral tegmental area (VTA), the origin of the dopamine 'reward' pathway that projects to the nucleus accumbens (N.Acc). Dopamine release in the N.Acc is usually concerned with naturally rewarding activities (such as eating, drinking, sexual activity, and so on), but addictive drugs can 'hijack' this system resulting in faster and greater amounts of dopamine release (NIDA, 2010). When nicotine activates the nicotinic receptors in the VTA, it results in massive dopamine release in the N.Acc (Corrigall et al., 1994).

In this way, nicotine and other addictive drugs are positively reinforcing – they tap into the normal instrumental learning mechanism which has evolved to ensure that pleasurable or rewarding activities are repeated. This mechanism, moreover, operates outside of conscious awareness, setting up a strong motivational drive to smoke, which may conflict with conscious thoughts, beliefs and plans. Negative reinforcement, by contrast, involves escaping from or avoiding aversive or unpleasant stimuli. Smoking also taps into this system – via the withdrawal syndrome. When a regular

questions

How important is the nicotine delivery in the maintenance of the smoking habit?

Why, given that e-cigarettes are almost certainly much safer than cigarette smoking, is there so much resistance to their use?

resources

West, R. (2006). *Theory of addiction.* Oxford: Wiley-Blackwell.
www.e-cigarette-forum.com/forum

references

Barrett, S.P. & Darredeau, C. (2012). The acute effects of nicotine on the subjective and behavioural responses to denicotinized tobacco in dependent male and female smokers. *Behavioral Pharmacology, 23*(3), 221–227.

Bullen, C., McRobbie, H., Thornley, S. et al. (2010). Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery. *Tobacco Control, 19*, 98–103.

Corrigall, W.A., Coen, K.M. & Adamson, K.L. (1994). Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. *Brain Research, 653*, 278–284.

Dawkins, L., Powell, J.H., West, R. et al. (2007). A double-blind placebo controlled experimental study of nicotine. II: Effects on response inhibition and executive functioning. *Psychopharmacology, 190*, 457–467.

Dawkins, L., Turner, J., Hasna, S. & Soar, K. (2012). The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition. *Addictive Behaviors, 37*(8), 970–973.

Doll, R., Peto, R., Boreham J. et al. (2004). Mortality in relation to smoking: 50 years' observation on male British doctors. *British Medical Journal, 328*, 1519–1533.

Etter, J.F. & Bullen, C. (2011). Electronic cigarette: Users profile, utilization, satisfaction and perceived efficacy. *Addiction, 106*(11), 2017–2028.

Etter, J.F. & Stapleton, J.A. (2006). Nicotine replacement therapy for long-term smoking cessation: A meta-analysis. *Tobacco Control, 15*, 280–285.

Hughes, J.R., Keely, J. & Naud, S. (2004). Shape of the relapse curve and long-

smoker stops smoking, they can experience aversive withdrawal symptoms (e.g. irritability, depression, restlessness, poor concentration, increased appetite) and strong urges to smoke. Nicotine ingestion, especially via smoking, extinguishes these symptoms.

Is the smoking habit just about nicotine ingestion?

Although the nicotine content is clearly a critical component of tobacco addiction, animal studies report that establishing reliable nicotine self-administration is more difficult than for other rewarding drugs such as heroin, cocaine and alcohol (Matta et al., 2007). A growing body of evidence also points to the role of non-nicotine factors in supporting smoking behaviour. Anecdotally, smokers prefer smoking to other forms of nicotine administration (e.g. patch, gum, nasal spray) and in the lab, smokers have been shown to prefer smoking a denicotinised cigarette over receiving intravenous nicotine (Rose et al., 2010). Smokers also report enjoying the sensory and tactile components of smoking, including the hand-mouth activity, taste, smell and sensations in the respiratory tract (Parrot & Craig, 1995) and if these sensations are removed, smoking satisfaction declines (Perkins et al., 2001). In fact, a number of studies have now reported that denicotinised tobacco smoking can alleviate nicotine withdrawal symptoms and craving (Rose et al., 2010) as well as elicit positive subjective effects comparable to smoking tobacco that contains nicotine (Barrett & Darredeau, 2012). Animal studies also show that nicotine administration is much stronger in the presence of sensory cues (e.g. a light or a tone; Sorge et al., 2009). So, nicotine in combination with other salient sensorimotor cues might be a particularly powerful recipe for the development of smoking addiction.

When a habit has been learned in the context of a particular set of cues (e.g. with a cup of coffee or tea; the sight and smell of smoke; the tactile sensation of a cigarette in the hand) these cues can then, via classical conditioning, act as 'secondary reinforcers' – they become moderately reinforcing in their own right. For example, the 'catch' in the throat associated with smoking, or manipulating a cigarette in one's hand, are unlikely to be pleasant in their own right, but smokers describe such things as pleasurable. It is likely that such sensations have been so closely associated with the primary rewarding effects of nicotine, that they have come to elicit a pleasant sensation and contribute to the process of smoking addiction. To borrow an example from West (2006): if we take a 20-a-day smoker who takes approximately 12 puffs on each cigarette – that person is repeating the reinforcement process 240 times a day, that is, 87,600 times a year and, if they continue to smoke for 25 years, that amounts to 2,190,000 times. Thus, it is easy to see how deeply entrenched the 'habit' can become and how cues closely associated with the primary reinforcer – nicotine – can come to be strongly reinforcing in their own right.

During a quit attempt, encountering a cue can be particularly troublesome

Cues may have a priming effect on the individual, that is, they whet the addict's appetite for the desired drug effect, inducing craving and motivation to use. During a quit attempt, encountering a cue (the sight or smell of a cigarette) can be particularly troublesome, making it more likely that craving and a lapse to smoking will occur. But how can cues elicit such strong control over behaviour? What's going on in the brain?

One well-accepted explanation (Robinson & Berridge, 1993) suggests that the dopamine reward pathway, which ordinarily mediates how 'noticeable' and 'attention grabbling' things are in the environment, becomes sensitised (more easily activated) because of the repeated exposure to nicotine. This means that when cues associated with smoking are encountered they become much more attention grabbing, salient and sought-after, causing increasing wanting and craving. This, in conjunction with the increasing evidence that smokers find it harder to inhibit over-learned tendencies (Dawkins et al., 2007), makes it extremely hard for the smoker to resist the urge to smoke (especially in the context of cigarette-related cues) during a quit attempt.

To recap, nicotine is positively reinforcing (it triggers dopamine release in the N.Acc) and abstinence from nicotine is punished (it is associated with withdrawal symptoms and craving). The strong association between the primary reinforcer, nicotine, and non-nicotine smoking-related cues (conditioned stimuli) results in strong secondary reinforcing processes. Part of the reinforcing process of smoking is likely therefore to include conditioned sensory and behavioural aspects of cigarette smoking (e.g. the handling of the cigarette, the 'catch' of smoke in the throat). The process of associative learning therefore results in a highly over-learned behaviour. Since the mechanisms underlying the conditioning process are unconscious, the smoker simply feels a powerful desire to smoke, which varies

term abstinence among untreated smokers. *Addiction, 99*(1), 29–38.

Hughes, J.R., Rennard, S.I., Fingar, J.R. et al. (2011). Efficacy of varenicline to prompt quit attempts in smokers not planning to quit. *Nicotine Tobacco Research, 13*(10), 955–964.

Kenny, T. (2012). *Smoking: The facts.* www.patient.co.uk/health/Smoking-The-Facts.htm

Matta, S.G., Balfour, D.J., Benowitz, N.L. et al. (2007). Guidelines on nicotine dose selection for in vivo research. *Psychopharmacology, 190*(3), 269–319.

NIDA (2010). *Drugs, brains, and behavior: The science of addiction.* tinyurl.com/bqvfbn8

Parrot, A.C. & Craig, D. (1995). Psychological functions served by nicotine chewing gum. *Addictive Behaviors, 20*(3), 271–278.

Perkins, K.A., Donny, E. & Caggiula, A.R. (1999). Sex differences in nicotine effects and self-administration: Review of human and animal evidence. *Nicotine and Tobacco Research, 1*, 301–315.

Perkins, KA., Gerlach, D., Vender, J. et al. (2001). Sex differences in the subjective and reinforcing effects of visual and olfactory cigarette smoke stimuli. *Nicotine and Tobacco Research, 3*, 540–546.

Robinson, T.E. & Berridge, K.C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Reviews, 18*: 247–291.

Roddy, E. (2004). Bupropion and other non-nicotine pharmacotherapies. *British Medical Journal 328*(7438), 509–511.

Rose, J.E., Behm, F. M., Westman, E.C. & Johnson, M. (2000). Dissociating

according to the presence of external cues as well as his or her internal state. Sensitisation of the dopamine reward pathway with chronic nicotine use establishes a heightened desire or craving for nicotine, especially in the presence of smoking-related stimuli. Thus nicotine addiction can be thought of as a deeply entrenched pattern of behaviour under powerful stimulus control because of repeated reward and punishment effects.

Efficacy of currently available 'quit smoking' aids

With the considerable evidence that smoking behaviour is driven by nicotine addiction and that nicotine itself is relatively safe, came the introduction of nicotine replacement therapy (NRT) – nicotine in the form of patch, gum, lozenge, inhalator and nasal spray. The rationale is to partially replace the nicotine derived from cigarette smoking thus alleviating craving and withdrawal symptoms and reducing the need to smoke. Over 100 placebo-controlled trials suggest that use of NRT doubles a smoker's chances of quitting successfully to 6–12 months (see Silagy et al., 2005, for a meta-analysis). However, given that the success rate for unaided quit attempts is so low, this means that, even with NRT, 93 per cent of quit attempts ultimately end in failure (Etter & Stapleton, 2006).

What about newer pharmacotherapies – Zyban (bupropion) or Champix (varenicline)? Zyban acts by increasing the availability of noradrenaline and dopamine thus mimicking the effect of nicotine and helping to reduce craving and withdrawal symptoms. Its success rate is comparable to NRT, doubling the chances of quitting successfully over placebo (Roddy, 2004). Champix partially activates the nicotinic acetylcholine receptors, helping to relieve symptoms of craving and nicotine withdrawal. It also prevents nicotine from activating these receptors so cigarette smoking does not trigger dopamine release, in turn reducing the motivation to smoke. A meta-analysis of placebo-controlled trials sponsored by the drug company suggests that it is three times better than placebo (Wu et al., 2006) with a 14 per cent success rate (Hughes et al., 2011). Champix however, has been associated with a number of side-effects, most worryingly psychiatric effects including agitation, depressed mood, suicidal thoughts and an increased risk of heart attack (see Siegel, 2011).

A 14 per cent success rate, even in the absence of side-effects, is still far from impressive. So why are these methods so unsuccessful? NRT and other pharmacotherapies address the nicotine addiction (by replacing it, mimicking it or preventing it from having its rewarding effects), but they lack the important sensory and behavioural cues associated with cigarette smoking. In other words, they do not address the associative learning processes that have occurred throughout a lifetime smoking habit. Rose et al. (2000) have shown that the combination of IV nicotine (which resembles the bolus of nicotine achieved from cigarette smoking) and smoking a denicotinised cigarette (which provides the sensory and behaviour aspects of smoking, CO and tar but no nicotine) produced effects similar to those of own-brand smoking.

What we need then is a device that replaces not only the nicotine from cigarette smoking, but also the 'activity' of smoking. If we could manufacture a device that could deliver nicotine effectively without the CO and tar *and* that mimicked the act of smoking – thus maintaining some of the secondary reinforcing aspects – maybe we would have a better method of helping smokers to quit. Perhaps such a device is already here?

Although the existing literature does not merit a conclusion that e-cigarettes are safe in absolute terms, they are clearly much safer than tobacco cigarettes

The electronic cigarette

Electronic cigarettes (sometime referred to as 'Electronic Nicotine Delivery Systems'; ENDS) are battery-operated devices that resemble cigarettes and deliver nicotine via inhaled vapour. Since their introduction into the market in 2004 by the Ruyan Group (also known as Dragonite) in China, electronic cigarettes (e-cigarettes) have gained popularity worldwide and are mainly sold via the internet. Removable cartridges (mouthpieces) contain glycerol or propylene glycol, flavouring, and varying amounts of nicotine. The nicotine

nicotine and nonnicotine components of cigarette smoking. *Pharmacology, Biochemistry and Behavior, 67*, 71–81.

Rose, J.E., Salley, A., Behm, F.M. et al. (2010). Reinforcing effects of nicotine and non-nicotine components of cigarette smoke. *Psychopharmacology, 210*, 1–12.

Siegel, M. (2011). *The rest of the story: Tobacco news analysis and commentary*. tinyurl.com/blgw643

Seigel, M. & Cahn, Z. (2010). *Evidence suggests e-cigs safer than cigarettes: Researchers claim.* tinyurl.com/cb86sza

Silagy, C., Lancaster, T. & Stead, L. et al. (2005). Nicotine replacement therapy for smoking cessation. The Cochrane Library, Issue 1. Chichester: Wiley.

Sorge, R.E., Pierre, V.J. & Clarke, P.B.S. (2009). Facilitation of intravenous nicotine self-administration in rats by a motivationally neutral sensory stimulus. *Psychopharmacology, 207*, 191–200.

Vansickel, A.R., Cobb, C.O., Weaver, M.F., & Eissenberg, T.E. (2010). A clinical laboratory model for evaluating the acute effects of electronic 'cigarettes'. *Cancer Epidemiology, Biomarkers & Prevention, 19*, 1945–1953.

Vansickel, A.R. & Eissenberg, T. (2012). Electronic cigarettes: Effective nicotine delivery after acute administration. *Nicotine and Tobacco Research*, Feb 6, doi:10.1093/ntr/ntr316

West, R. (2006). *Theory of addiction*. Oxford: Wiley-Blackwell.

Wu., P., Wilson, K., Dimoulas, P. & Mills, EJ. (2006, 11 Dec). Effectiveness of smoking cessation therapies. *BMC Public Health, 6*, 300.

solution is vapourised by the heating element/atomiser which is activated by 'drawing' on the device or pressing a button. 'Smoking' an electronic cigarette (often referred to as 'vaping') therefore mimics the act of smoking: the user holds the device and draws on it like a cigarette; the vapour produced resembles smoke and is drawn into the lungs and exhaled like smoke; tobacco (or menthol) flavouring resembles the taste of inhaled tobacco smoke. In short, it addresses the sensory and behavioural components of smoking that are being increasingly recognised as important contributors to the reinforcing effects of smoking (see Rose et al., 2010). Furthermore, since no tobacco is burned, inhaling nicotine in this way has the potential to provide a safer alternative to cigarette smoking since it eliminates the harmful tars and carbon monoxide associated with smoking. Nevertheless, uncertainty remains concerning efficacy of nicotine delivery via e-cigarettes and how they should be regulated.

E-cigarettes are already banned in some countries (including Australia, Thailand, Brazil) and cannot be imported into others (Canada). These same countries however, continue to sell tobacco – 'the only consumer product that will kill half its users when used as intended' (smokefree.org.nz/face-facts). Both the World Health Organization (WHO) and the US Food and Drug Administration (FDA) have voiced concerns over the contents of the cartridges, the properties of the vapour, and whether the products are safe or effective. In the absence of clinical controlled trials, they have asked manufacturers not to make cessation claims, and the Royal Pharmaceutical Society has recently announced that physicians should not recommend them to their patients. The EU is currently consulting over regulation and the MHRA (Medicines Health Regulatory Authority) will decide this year whether to ban, regulate or do nothing.

In 2009 the FDA conducted a chemical content analysis of 19 e-cigarette cartridges and reported the presence of diethylene glycol (a poison) and tobacco-specific nitrosamines (TSNAs; known cancer-causing agents) in some of the cartridges, as well as inaccurate reporting of nicotine content. What it failed to mention however, was the maximum level of nitrosamines found in e-cigarettes was comparable to that found in nicotine replacement therapies. TSNA levels present in cigarettes, by comparison, are 1000 times this level (Siegel & Cahn, 2010).

Let's face it, inhaling any chemical into the lungs is likely to be associated with some harm, but compared to the multiple known health risks associated with cigarette smoking which kills 81,700 people per year in England alone, the health risks of the non-combustible e-cigarette is likely to be in orders of magnitude lower. Following a review of the literature, Professor Siegel from Boston University concluded that although the existing literature does not merit a conclusion that e-cigarettes are safe in absolute terms, they are clearly much safer than tobacco cigarettes. In fact, 'the truth is we know a lot more about what is in electronic cigarettes than in regular cigarettes' (Siegel & Cahn, 2010).

Can the e-cigarette help smokers to quit?

Although a product that delivers nicotine and incorporates the sensory and behavioural aspects of smoking has considerable potential to reduce the public health burden associated with tobacco smoking, smokers are only likely to switch to e-cigarettes if they are easy to use, effectively replace the primary and secondary reinforcing aspects of smoking and can reduce nicotine craving and withdrawal symptoms. Whist clinical trials have yet to be completed, a recent large online survey reported over 90 per cent of users stated that e-cigarette use had helped them to quit smoking or reduce their cigarette consumption (Etter & Bullen, 2010). Two published reports of e-cigarette use in naive users, however, showed inefficient nicotine delivery (Bullen et al., 2010; Vansickel et al., 2010), although craving and (to a lesser extent) withdrawal symptoms were alleviated. A reduction in craving and withdrawal symptoms in the absence of raised blood nicotine levels is consistent with the notion discussed earlier that other sensorimotor factors associated with smoking contribute to its reinforcing effects.

> "we know a lot more about what is in electronic cigarettes"

In a study conducted in our lab at the University of East London (Dawkins et al., 2012), abstinent smokers given a 0 mg (placebo) e-cigarette reported comparable reduction in craving and withdrawal symptoms after five minutes of use to those given 16 mg nicotine. After 20 minutes, compared with the placebo group, craving and withdrawal symptoms were further reduced in males but not females receiving nicotine. These gender differences are consistent with an emerging body of evidence suggesting that the smoking behaviour of men may be reinforced more by nicotine intake, and in women more by non-nicotine-conditioned responses to smoke stimuli (Perkins et al., 1999). We also observed an improvement in working memory with nicotine (relative to placebo) in the whole sample, suggesting that nicotine delivery is at least sufficient to improve the mild cognitive impairment often observed during abstinence.

Interestingly, in a recent study of experienced vapers using their own devices, Vansickel and Eissenberg (2012) demonstrated significantly elevated blood nicotine levels, comparable to those achieved via cigarette smoking. This latter study clearly suggests that e-cigarettes are capable of delivering adequate levels of nicotine but that new users may need to overcome a learning curve with regard to the nature of vaping and product choice.

To conclude

Increasing evidence suggests that people smoke for both the nicotine and the non-nicotine, sensorimotor (conditioned) effects. Current pharmacotherapies for smoking cessation address only the former. The e-cigarette delivers nicotine without tobacco combustion and mimics the act of smoking, thus replacing some of the important sensorimotor aspects of smoking. It therefore has the potential to provide pleasure as well as save lives. Whilst survey results suggest that e-cigarettes are a highly effective nicotine replacement, such respondents are likely to be positively biased and we await the results of clinical trials to determine whether this promising new device can indeed improve our current arsenal of smoking cessation techniques.

The health risks and safety aspects of e-cigarettes are a frequently – and sometimes sensationally – expressed concern. On balance, however, e-cigarettes are probably doing people very little harm and, in all likelihood, doing people a lot of good if they are using these as a complete or partial alternative to tobacco smoking. What is very apparent is that the potential to contribute to improved public heath certainly merits further research.

Lynne Dawkins
is a Senior Lecturer at the University of East London
l.e.dawkins@uel.ac.uk