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Nicotine dependence: why is it so hard to quit?

COLIN MENDELSOHN MB BS(Hons)

Most smokers repeatedly fail to quit because they are addicted to nicotine and have lost control of their smoking behaviour. This article examines why it is so hard to break the habit long term and suggests strategies GPs can use to optimise their interventions. Smokers need to be re-engaged and assisted through repeated attempts to quit over the long term.

Key points

- Nicotine dependence is a substance abuse disorder involving compulsive drug use in spite of known health risks.
- Most smokers continue to smoke because they are addicted to nicotine. Today's smokers may be more addicted than in the past.
- The psychoactive effect of nicotine is mediated by activation of the powerful reward pathway in the brain and the release of dopamine.
- Other mechanisms underlying nicotine addiction are environmental cues, nicotine cravings and withdrawal symptoms.
- Successful treatment is based on optimising pharmacotherapy and behavioural strategies to counter smoking cues.

Smoking is the single greatest cause of preventable illness and death in Australia. About half of all lifelong smokers die prematurely from their habit and smokers live 10 years less on average than nonsmokers.[1]

The vast majority of smokers in Australia want to quit,[2] and most make repeated attempts to do so. About 40% try to stop smoking at least once each year.[3]

However, long-term quitting is an elusive goal for many smokers. Only 3 to 5% of unaided quit attempts are successful six to 12 months later.[4] Even with professional counselling and pharmacotherapy, only 28% of smokers are abstinent at six to 12 months.[5] About 40% of smokers in Australia are unwilling or unable to quit before the age of 60 years.[6] Even among those who do quit, there is a steady attrition over time. After 12 months, about half of all quitters will subsequently relapse.[7]

Most smokers repeatedly fail to quit because they are addicted to nicotine. Nicotine has been rated by drug addicts as the most difficult drug of all to give up.[8]

Smoking is coded in disease classifications as a substance abuse disorder.[9,10] Similar to other drug addictions, it is defined as the compulsive taking of a drug in spite of harmful effects. The key features of addiction that apply to smoking are:

- a withdrawal syndrome on cessation of the drug
- repeated, unsuccessful attempts at quitting

Dr Mendelsohn is a General Practitioner in Sydney with a special interest in smoking cessation. He is also the editor of *Your Health Newsletter* and a member of the Executive Committee, Australian Association of Smoking Cessation Professionals.

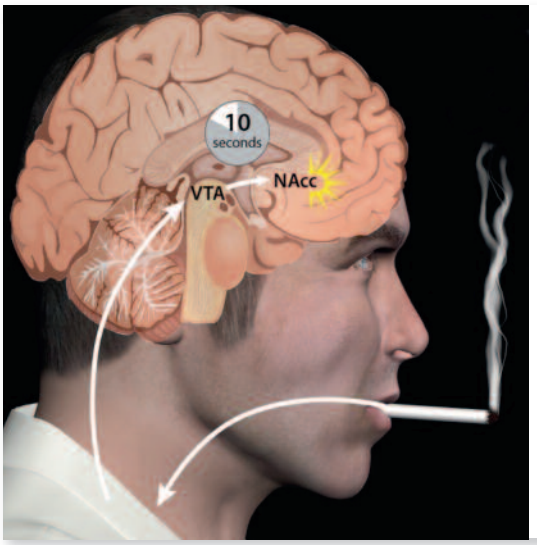

Figure 1. The mesolimbic reward pathway. Nicotine activates the nicotinic receptors in the ventral tegmental area in the midbrain within 10 to 19 seconds of inhalation, triggering the release of dopamine in the nucleus accumbens.

ABBREVIATIONS:
NAcc = nucleus accumbens;
VTA = ventral tegmental area.

NICOTINE WITHDRAWAL SYNDROME[9]

Includes four or more of the following:

- dysphoric or depressed mood
- insomnia
- irritability, frustration or anger
- anxiety
- difficulty concentrating
- restlessness or impatience
- decreased heart rate
- increased appetite or weight gain

- continued use in spite of known health risks.

This article examines the underlying mechanisms of nicotine addiction, including important genetic and neurochemical factors. Understanding nicotine dependence has important implications for the GP's attitude to patients who smoke and helps inform a rational approach to treatment.

ADOLESCENT UPTAKE

Eighty per cent of adult smokers start smoking before 18 years of age.[11] Adolescents are more sensitive than adults to nicotine and develop dependence more quickly and from lower levels of nicotine intake.[12] Among teenagers who lose control over their tobacco use, 10% do so within two days of inhaling from a cigarette for the first time and 25% within 30 days.[12] Symptoms of nicotine dependence develop in 70% of adolescents before they are smoking daily.[13]

Children whose mothers smoked during pregnancy are also more likely to become dependent on tobacco if they start smoking.[14]

ROLE OF GENETICS

Twin studies have indicated that genetic factors account for 60 to 70% of the chance of becoming nicotine dependent after starting to smoke.[15,16]

The cytochrome P450 *CYP2A6* gene is responsible for the metabolism of about 90% of nicotine. Variations in the gene determine the rate of nicotine breakdown, which can vary by up to fourfold. Slower metabolisers have lower nicotine dependence, smoke fewer cigarettes, respond better to nicotine replacement therapies and are able to quit more easily.[17,18]

Rates of nicotine breakdown also vary considerably across gender and race. For example, men metabolise nicotine more slowly than women and Asian populations are slower metabolisers of nicotine than Caucasians.[17]

Genes affecting the sensitivity of nicotine receptors and the reward pathway have also been identified.

REWARD PATHWAY

Similar to other drugs of abuse, such as cocaine and heroin, nicotine activates the mesolimbic reward pathway, releasing dopamine. Dopamine creates the pleasurable sensations associated with smoking that are central to its addictive properties and lead to further drug-seeking (nicotine) behaviour (Figure 1).[19]

Dependence on nicotine is reinforced further by the repeated and very rapid exposure to the drug. The 20 cigarette-a-day smoker gets 200 hits of nicotine every day and each bolus of nicotine reaches the brain within 10 to 19 seconds of inhalation.[18] Chronic nicotine exposure upregulates nicotinic receptors. Over time there are more receptors releasing dopamine, making quitting even more difficult.[20]

Within a few hours of the last cigarette the smoker experiences nicotine withdrawal symptoms due to reduced dopamine levels. The unpleasant psychological and physical symptoms of the nicotine withdrawal syndrome can be relieved by smoking and are a powerful trigger for early relapse (see the box on this page).[9]

A reduction in nicotine levels in the brain also leads to background cravings for nicotine, which are also an important cause of relapse in the first week of quitting.[21] Smokers regulate their smoking behaviour to maintain their blood nicotine level within a comfortable range to avoid cravings and withdrawal symptoms.

As well as dopamine, nicotine triggers the release of a range of other neurotransmitters that also play a role in nicotine addiction (Figure 2).[22]

OTHER MECHANISMS UNDERLYING NICOTINE DEPENDENCE

Cue-induced cravings

Specific behaviours and situations, such as drinking a cup of coffee or the smell of smoke, are associated with smoking and the pleasurable effects of the behaviour. This creates a conditioned or learned

response so that exposure to the smoking cue can trigger a strong urge to smoke, especially in women.[19,21]

Desire for the positive effects of nicotine

As well as pleasure, nicotine can generate arousal, heightened alertness, relief of anxiety or depression, reduced hunger and control of body weight. It is used by smokers for these effects (Figure 2).[22]

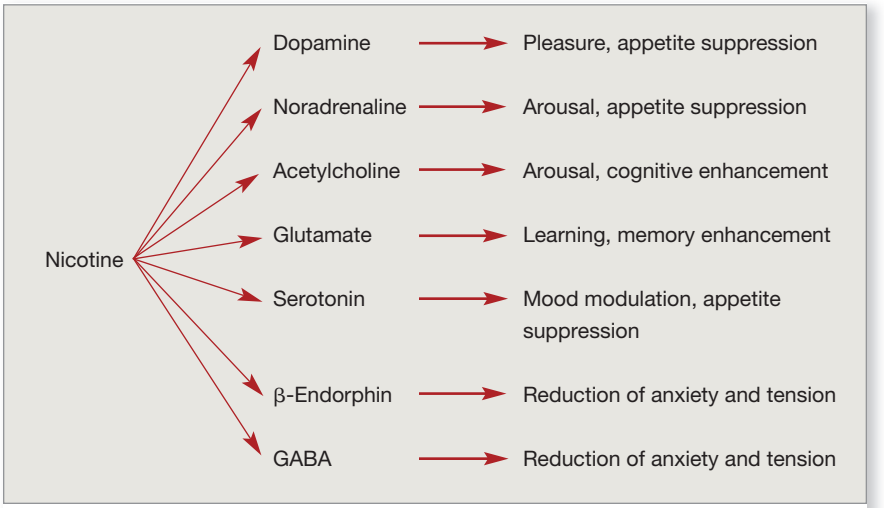

Figure 2. Neurotransmitter release triggered by nicotine.[22]

LIGHT AND NONDAILY SMOKERS

Light (10 or less cigarettes per day) and nondaily smokers are a growing proportion of smokers. In 2010, 16.4% of smokers in Australia did not smoke every day.[6] These smokers tend to smoke more for the positive effects of nicotine and in response to smoking cues, such as in social situations.[23]

However, numerous studies have shown that many low-level smokers experience nicotine withdrawal and other indicators of nicotine dependence.[24] This is important because even the presence of a single symptom can affect quitting.[24]

Low-level smoking is not harmless. Significant health risks are associated with light smoking. Smokers of one to four cigarettes per day almost triple their risk of dying from ischaemic heart disease compared with never smokers (odds ratio, 2.84) and have a 50% increased mortality from all causes (odds ratio, 1.52).[25]

IS NICOTINE HARMFUL?

Although nicotine is the main cause of dependence on tobacco, it is not carcinogenic, does not cause respiratory disease and has only minor haemodynamic effects.[26] However, it can delay wound healing, increase insulin resistance and is associated with harmful effects on the fetal brain[27] and lungs.[28]

THE 'HARDENING' HYPOTHESIS

There is some evidence to support the 'hardening' hypothesis that proposes that smokers who have found it easy to quit have already done so, leaving a more resistant group for whom quitting is more difficult. Although this seems logical, a recent review suggests that more research is needed to verify it.[29]

People with mental health disorders now form an increasing core of the remaining smokers. They are twice as likely to smoke than other people and also smoke more heavily. This group is more dependent on nicotine than other smokers, has lower quit rates and is often neglected by health professionals.[30]

Countries with low smoking rates such as Australia have higher nicotine dependence levels and smokers find it harder to quit.[31]

CLINICAL IMPLICATIONS

Continuing smokers are not weak willed nor are they simply making a bad life-style choice. Rather, they are victims of a potent drug addiction mediated by powerful neurochemical processes, often with an underlying genetic predisposition. In nearly all cases, the addiction has already developed in adolescence. Smokers deserve an empathic, nonjudgemental and supportive approach.

Although some smokers can quit without help, many individuals need assistance, especially those with higher levels of nicotine dependence. Similar to addicts to other substances, smokers have lost control of their behaviour and medical treatment is often essential and appropriate.

However, many light and nondaily smokers are also nicotine dependent and are at-risk of smoking-related diseases. Nondaily smokers are more likely to want to quit than daily smokers but are less likely to be advised to quit by their doctors.[32] This group should be informed that no level of smoking is safe. They should be advised to stop smoking and offered assistance including help with smoking cues. Pharmacotherapy may sometimes have a role.

Reducing the number of cigarettes or changing to lighter cigarettes are not effective strategies in dependent smokers because they typically compensate by varying their puff frequency and depth to maintain the nicotine level within a certain range.

Smoking (nicotine dependence) is now classified as a chronic medical disease,[9,10] with multiple cycles of relapse and remission. Similar to patients with poorly controlled diabetes, relapsed smokers need to be re-engaged and assisted through repeated attempts to quit over the long term.

TABLE 1. FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE[33]

	Questions	Answers	Points
1.	How soon after you wake up do you smoke your first cigarette?	Within 5 minutes 6 to 30 minutes 31 to 60 minutes After 60 minutes	3 2 1 0
2.	Do you find it difficult to refrain from smoking in places where it is forbidden (e.g. in church, at the library, in cinemas, etc)?	Yes No	1 0
3.	Which cigarette would you hate most to give up?	The first one in the morning All others	1 0
4.	How many cigarettes do you smoke each day?	10 or less 11 to 20 21 to 30 31 or more	0 1 2 3
5.	Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes No	1 0
6.	Do you smoke if you are so ill that you are in bed most of the day?	Yes No	1 0

A score of 0 to 2 = very low dependence; 3 to 4 = low dependence; 5 = medium dependence; 6 to 7 = high dependence; 8 to 10 = very high dependence.[36]

Effective intervention is based on the smoker's readiness to quit. Different strategies are required for smokers who are not ready, unsure or ready to quit.[33]

ASSESSING NICOTINE DEPENDENCE

Assessment of nicotine dependence helps predict whether the smoker will experience nicotine withdrawal symptoms and is a guide to the intensity of treatment required. In the clinical setting, the single most reliable indicator is the time to first cigarette.[34] As most nicotine is cleared overnight (the half-life of nicotine is two hours), smokers wake in a state of nicotine deprivation. Acting quickly to replenish nicotine levels is a sign of dependence.

Cravings and withdrawal symptoms experienced in previous quit attempts are also a useful guide to nicotine dependence.

The number of daily cigarettes is less useful because self-reports are often unreliable, cigarette brands differ in strength, and smoking behaviour and nicotine metabolism vary from one smoker to the next.

Nevertheless, the risk of nicotine dependence rises with higher levels of use.[35] Smoking more than 15 cigarettes per day is generally associated with a greater likelihood of dependence.[34]

The Fagerström Test for Nicotine Dependence is a more detailed and well-validated tool to measure the level of addiction. It is a good predictor of withdrawal symptoms and successful quitting (Table 1).[33,36]

PHARMACOTHERAPY

Guidelines recommend using pharmacotherapy for all nicotine-dependent smokers.[5,33] First-line medications (nicotine replacement therapy, varenicline and bupropion) increase success rates by two to three times those of placebo.[5] In view of the potency of nicotine addiction, it is important to optimise the use of pharmacotherapy (Table 2).[5,37-41]

Background nicotine cravings and withdrawal symptoms are relieved by all forms of smoking pharmacotherapy and settle within a few weeks of cessation. Cue-induced cravings, however, can persist for many years after quitting and are a common cause of early and late relapse. They are alleviated by fast-acting forms of nicotine replacement therapy such as gum or lozenge but not by the nicotine patch.[41-43]

Some smokers who are highly addicted and cannot choose to stop smoking, may benefit from harm reduction with long-term nicotine replacement therapy to reduce the risk of smoking-related disease,[44] although this is controversial.

COUNSELLING

The best results are achieved when pharmacotherapy is combined with counselling. Even minimal interventions are effective in increasing cessation rates.[33,45] However, more intensive interventions with multiple sessions are most effective and longer counselling sessions are more successful than shorter ones. In view of the high risk of early relapse, smokers need the most support in the first week or two after quitting.[4]

It is advisable to help smokers develop coping strategies to deal with high-risk situations and specific smoking cues after quitting.[33,43] For example, a smoker could plan to drink tea instead of coffee if the latter triggers an urge to smoke. Avoiding other smokers for the first week or two after quitting is also sensible advice.

It is also important to assess the individual smoker's barriers to quitting and develop strategies to overcome them. Common barriers are withdrawal symptoms, stress, fear of failure, social pressure and weight gain. Support from family

TABLE 2. HOW TO OPTIMISE PHARMACOTHERAPY

Treatment	Description	Odds ratio (95%CI)	Follow up
Combination NRT	Combination NRT (nicotine patch plus fast-acting NRT, e.g. gum, lozenge, spray) is safe, well tolerated and more effective than monotherapy	1.9 (1.3 to 2.7)[5] (Compared with nicotine patch alone)	6 months
	Nicotine patch plus bupropion	1.3 (1.0 to 1.8)[5] (Compared with nicotine patch alone)	6 months
Prequit treatment with nicotine patches	Start the nicotine patch two weeks before quit day, rather than starting on quit day	2.17 (1.46 to 3.22)[37] (Compared with starting on quit day)	6 months
Varenicline	The most effective single agent	1.13 (0.94 to 1.35)[38] (Compared with nicotine patch alone)	6 months
		1.52 (1.22 to 1.88)[38] (Compared with bupropion alone)	1 year
	A second course in smokers who have quit increases long-term success rates	1.34 (1.06 to 1.69)[39] (24-week course compared with 12 weeks)	1 year
Lapse prevention	Continue nicotine patch after a lapse to prevent progression to relapse	5.56 (2.3 to 9.1)[40] (Compared with stopping the patch after a lapse)	3 weeks
	Fast-acting NRT (e.g. gum) to treat cue-induced cravings	Significantly greater craving reductions compared with placebo gum[41]	N/A

ABBREVIATIONS: CI = confidence interval; NRT = nicotine replacement therapy.

and friends increases success rates and should be encouraged.[33]

CONCLUSION

Smoking is now viewed as a powerful substance abuse disorder. Most smokers continue smoking because they are addicted to nicotine and have lost control of their smoking behaviour.

Nicotine dependence is mediated by powerful neurochemical processes and an underlying genetic predisposition that makes it extremely difficult for many smokers to quit, especially as today's smokers may be more nicotine dependent than in the past.

Similar to other victims of serious, chronic disease, smokers need our empathy and support over the long term. Intervention is a vital and appropriate function for GPs.

Effective treatment begins with assessing the level of nicotine dependence. Optimal therapy includes maximising the use of medication for all nicotine-dependent patients, intensive support and behavioural change to counter the conditioned response to smoking cues. MT

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COLIN MENDELSOHN MB BS(Hons)

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