

What's new in *Nicotine & Tobacco Research*?

Edited by Richard Hébert

Original Articles

Stimulating dopamine to curb smoking

Animal studies have shown that nicotine releases dopamine in brain areas associated with reward, and that animals will self-administer intravenous nicotine, but few human studies have tested whether dopamine is involved in mediating nicotine intake. Caskey *et al.* (p. xxx) tested a dopamine agonist ('stimulant') and a dopamine antagonist ('blocker') on 20 people who smoked heavily, in two sessions lasting up to 6 h each. The subjects were asked to smoke whenever they wanted, but to smoke using a puff-measuring device. In one session they were administered the dopamine 'stimulant' bromocriptine, a drug used to treat Parkinson's disease, among other conditions; in the other session they were administered haloperidol, an anti-psychotic medication that 'blocks' dopamine.

The investigators found that when dopamine was blocked, the subjects smoked more cigarettes and smoked them faster, their puffing time was significantly higher, they took significantly more puffs, and they reported higher craving levels relative to when dopamine was 'stimulated' with bromocriptine. Under dopamine stimulation, however, they also experienced more nausea, which may have accounted for part of their reduced smoking; however, the researchers reported 'a substantial . . . effect (on smoking behavior) independent of nausea'. Overall, they said, their results 'imply that smoking behavior can be manipulated within the same subjects in opposite directions by alternately stimulating and blocking dopamine, which strongly suggests the importance of dopamine in reinforcement from cigarette smoking.'

Spit tobacco: can anti-depressants help?

Although nicotine patches, nicotine gum, and the anti-depressant bupropion have all been shown to be effective

in helping cigarette smokers quit, effective pharmacological treatments for spit tobacco (ST, or smokeless tobacco) users have not been identified. In the first randomized, placebo-controlled clinical trial evaluating bupropion for ST users, Dale *et al.* (p. xxx) tested the drug on 68 subjects. They were told to stop using ST a week after starting the medication. Thirty-one dropped out of the study during the 12-week medication phase; these were included in the results. Forty-four per cent of those on bupropion but only 26% of those on a placebo were still abstinent at the end of the 12 weeks. At 24 weeks after starting the medication, abstinence rates were at 29% for both groups. Bupropion also had positive effects on weight gain early in the pilot study, but this disappeared by the 6-month follow-up. They also found that withdrawal symptoms increased in both groups for the first 6 weeks then declined among those on bupropion.

The authors said that their results 'support proceeding with a larger, multi-center, randomized controlled clinical trial to determine the efficacy of bupropion' for ST users, perhaps involving administering the drug longer than 12 weeks. 'Other studies combining nicotine replacement with bupropion should be conducted' to see if more aggressive management of withdrawal symptoms might boost abstinence rates.

Still elusive: nicotine's arousal effects

It is known that nicotine acts on neurotransmitters that trigger arousal and activation, but how this manifests in the various stages of information processing is not yet clear. Davranche and Audiffren (p. xxx) tested 16 'slightly dependent' smokers who used light-dosage (7-mg) nicotine patches; the researchers assessed the effects of the patches on cognitive processes, including when subjects were drowsy after lunch, and in conditions while they watched a succession of calm, 20-min-long documentaries in a warm, darkened room.

Beginning in mid-afternoon, 6 h after the patches were applied, the subjects reported higher states of alertness when receiving nicotine than when they were on the

Correspondence to: Dr Gary E. Swan, Center for Health Sciences, 333 Ravenswood Avenue, Menlo Park, CA 94025, USA

placebo patch, despite the monotony of the reaction tests they were undergoing. The benefit persisted through the afternoon. In the tests, the subjects responded to both clear and degraded visual stimuli on a computer screen by activating two levers. The stimuli were preceded by an audible warning. Again, not until 7 h after the patches were applied were differences noted: accurate responses came more quickly on nicotine than on placebo despite the drowsiness-inducing afternoon conditions and regardless of the amount of advance warning (arousal) or the quality of the visual signal (activation), both contrary to expectations. The subjects were also asked to distinguish between higher and lower frequencies of flickering lights on a screen, but again, contrary to expectations, no nicotine effects were found.

The researchers suggest that the absence of predicted results was due to the low dosage and the method of administering it. 'Everything points to the fact that certain substances, such as nicotine, generate easily observed reactions at a biological level,' they wrote, 'but . . . the repercussions . . . are difficult to observe on a purely behavioral level for such low doses administered progressively.'

Self-report bias: how much, how long

Discrepancies between self-reports of non-smoking by subjects in clinical trials, and the biochemical evidence – cotinine in saliva or expired carbon monoxide – used to verify those self-reports, continue to concern investigators. Murray *et al.* (p. xxx) analyzed data from the Lung Health Study, a randomized trial in 10 North American clinical centers that collected smoking status records over 5 years from 3923 adults enrolled in a smoking intervention program and 1964 in usual care. Among their findings:

- Discrepancies were small and improved over the years, but they did continue. The improvement was 'both clearer and more persistent' with carbon monoxide than cotinine.
- About half of those in the smoking intervention program who said they were not smoking, although cotinine testing indicated otherwise, continued to exhibit a 'social desirability' bias over the 5 years. Overall, carbon monoxide testing showed less bias.
- Some discrepancies appeared to be attributable to subjects' learning that they can manipulate carbon monoxide readings by not smoking for a few hours before the test, but this is less effective on cotinine, which has a longer half-life in the body.
- Self-reports contradicted by carbon monoxide testing tended to be by males, particularly those with lower levels of education and those with more smokers at home.
- Self-reports contradicted by cotinine testing were characteristic of those who were older, married, and who said at baseline that they were light smokers or did not drink alcohol.

'Our . . . results indicate that about half of self-report bias across time is attributable to a single subset of individuals,' the authors concluded. 'A study that includes personality measures, for example, may improve our understanding of the mechanisms involved. We also found that overall bias tends to decrease over time. . . . Although biochemical verification has come to be regarded as the norm for smoking studies, these results are essentially good news for studies that rely on self-report.'

Devalued costs and rewards: weighing delays

Studies have shown that people (and non-humans) value an immediate reward more than they value a delayed reward, even if the rewards are equal. The same is true of costs: an immediate cost is considered more expensive than an equal one that is delayed. In both cases, the delayed reward or cost is devalued or discounted. No study, however, had yet examined how smokers and non-smokers value delayed and immediate benefits and losses. To fill that gap, Odum *et al.* (p. xxx) tested 23 smokers, 21 former smokers and 22 subjects who had never smoked. They found:

- Smokers devalued delayed health gains more quickly than either of the other groups. For example, they considered 10 years of gained health delayed by a year as worth only 7.75 years, but it was worth 8.85 years of health to those who had never smoked.
- Delayed health losses lost value even more rapidly for smokers. Delaying 10 years of bad health by 1 year cut its value in half for smokers, but only reduced it to 8.25 years for the non-smokers.

'Perhaps the most intriguing finding,' the investigators report, '. . . [is that] [s]mokers and ex-smokers discounted health losses more steeply than health gains,' suggesting that 'in some cases appeals to future health problems (e.g., lung cancer, emphysema) could be less effective in encouraging abstinence than appeals to future health benefits (e.g., increased fitness and longevity).'

Cotinine test strips pass test

Biochemical tests to confirm self-reports of smoking have had their drawbacks. Measuring carbon monoxide in expired air is easy and quick, but levels can be influenced by diet, time of day, physical activity, and exposure to pollution. Measuring cotinine, a major metabolite of nicotine, in urine, blood, or saliva is far more accurate, given that it is directly proportional to the quantity of nicotine absorbed and has a much longer half-life; but until now this has been both costly and time-consuming.

A cotinine-detecting test strip has now been developed and tested. The NicoMeter™ urine test is simple to use

and relatively inexpensive, and yields results in minutes. Parker *et al.* (p. xxx) compared the test results from the urine samples of 256 subjects at Memorial Hospital of Rhode Island, using both the prototype strips and gas chromatography. They found that the strips agreed with the gas chromatography method in identifying smokers better than 97% of the time, and identified non-smokers 'with a fair-to-moderate level of agreement' 74.5% and 86.4% of the time, depending on which of two cut-off points was employed.

The test strip has been further developed and is now commercially available. Using the prototype test strips, however, the investigators reported, 'If the goal of (using) the test strip is to have a simple, inexpensive, and rapid measure to immediately confirm smoking status in field settings, then the test strip may be appropriate. If the main objective is to confirm smoking status for the evaluation of an intervention, then other techniques (e.g., gas chromatography) should be selected.'

The price of a smoker's life

Smoking will kill about 10 million people a year worldwide by the 2020s or early 2030s. Some studies suggest that half of all regular smokers who started as adolescents will eventually die from smoking. Others say one-third. What would it cost to save those lives, given current knowledge?

Ranson *et al.* (p. xxx) calculated for three interventions the public-sector costs per year of healthy life saved (called DALYs – disability-adjusted life years), using conservative assumptions – from the one-third figure for likely deaths to assigning substantial costs even to zero or low-cost stroke-of-the-pen interventions.

- 1 *A 10% price increase in cigarettes:* The most cost-effective strategy, at \$12–\$313 per DALY, would save five to 16 million lives worldwide (1–4% of deaths expected among all 1995 smokers). Young people, those most price-sensitive, would benefit disproportionately. About 13% of deaths would be avoided among smokers who were 15–29 years old in 1995, compared to 6% among those aged 20–29, and 2–3% among those aged 30–49.
- 2 *Nicotine replacement therapies (NRT):* The cost estimate per DALY saved is between \$358 and \$1917, depending on several variables; even if only 1 in 20 smokers on NRT succeeded in quitting, about 1 million smoking-attributable deaths would be averted.
- 3 *Non-price and non-NRT interventions:* A hypothetical package that includes a total ban on advertising, a public information campaign, and smoking restrictions in public and work places, individually shown to have had 2–10% effectiveness in the USA, would cost between \$145 and \$2896 per DALY saved, depending on assumptions. Even a 2% quit rate would prevent 5 million deaths, again with the greatest impact among

younger smokers, with about one-third of averted deaths among those aged 20–29 in 1995.

In each scenario, low- and moderate-income countries garner 80–90% of the avoided deaths. Because of this, the cost per DALY would be three to eight times higher in high-income countries for NRT, 20 times higher for non-NRT and non-tax interventions, and almost 40 times higher for tax increases, all of them still relative bargains. By comparison, one study estimated that the most cost-effective intervention for reducing coronary risk factors costs \$496–1488 per DALY for men and \$1760–5536 for women. The investigators caution, however, that their estimates 'are subject to considerable variation in actual settings, notably in costs; thus local cost-effectiveness studies are required to guide local policy.'

Growing up: why few quit, many do not

For many, the years from late adolescence to early adulthood are a time of exploration and change, when risky behavior peaks and then declines, with the notable exception of smoking. Tucker *et al.* (p. xxx) investigated this anomaly by following a diverse group of 711 young adult smokers for 5 years, beginning when they were high school seniors. By the end of that period, only 96 said they had quit smoking. The researchers explored a wide range of social environment, beliefs and behavioral variables to see what distinguished those who quit from those who did not. Among the findings:

- More males (but not females) quit if they had received fewer cigarette offers as high school seniors, even though females reported getting more such offers, suggesting that male smokers find it harder to resist social pressure to smoke.
- More females quit if, when they were seniors, they believed their parents disapproved of their smoking and they had fewer friends who smoked. However, the converse was not true: parental smoking and peer disapproval were not important factors.
- Females who believed they could not resist the temptation to smoke were less likely to quit.
- Male smokers were less likely to quit if their parents had been divorced.
- Both males and females were less likely to quit if they received poor grades as seniors.
- Unexpectedly, adolescent rebelliousness and problem behavior were not significant barriers to quitting, although they were risk factors for starting to smoke.
- Although emotional distress is also a significant predictor that an adolescent will start smoking, poor mental health did not seem to be a barrier to quitting. (Further research is needed to clarify the role of mental health.)
- Oddly, many of the associations for women could be explained by how often they smoked, but that was not the case for the men.

On the trail of genetic predisposition

Nicotine addiction appears to result from the drug's ability to bind with receptors in the brain and trigger a reward mechanism that involves dopamine neurotransmission. Because the dopamine transporter (DAT) gene plays a central role in reuptake of released dopamine, variation in that gene – particularly a variable number of tandem repeats (VNTR) polymorphism often found in sequences of nine or 10 copies – is a prime suspect.

Vandenbergh *et al.* (p. xxx) looked for that VNTR in the DNA from 595 cheek swabs submitted by a national sample of volunteers, then matched the results to smoking status self-reports. When they compared current and former smokers to non-smokers using the standard government definition of *non-smoker* (never having smoked at least 100 cigarettes in one's lifetime), they found no significant relationship. Only when they separated true never-smokers from those who had smoked fewer than 100 cigarettes did a trend emerge, but it was in the opposite direction from what they had expected. Previous research showed that those with the nine-copy allele of the VNTR were both *less* likely to have started smoking before age 16 and *less* likely to be smokers. Instead, Vandenbergh *et al.* found no relationship with the age at which the smoker had started. They noted that, compared to those who had never smoked, persons with the nine-copy allele were 1.81 times *more* likely to have ever smoked fewer than 100 cigarettes and even *more* likely to be current smokers. The authors concluded that studies should distinguish between never-smokers and non-smokers who smoked fewer than 100 cigarettes, a distinction that they note is 'particularly important for genetic studies to assess predictors.'

Present understanding of the role of genetics in smoking is 'quite limited,' they wrote. 'It is likely that any effects of DAT on smoking depend on a host of other genetic influences. . . . Any relationship between a single gene . . . and smoking is expected to be complex and difficult to characterize. This difficulty does not diminish the importance of identifying the genes involved in smoking-related behaviors and speeding the development of successful pharmacological and behavioral interventions to reduce the substantial morbidity and mortality caused by smoking tobacco.'

Nitric oxide: nicotine's sidekick

It is likely that there is more to the addictive hook of cigarette smoke than simply nicotine. A strong candidate for nicotine's chief co-conspirator is nitric oxide (NO), both what is inhaled in cigarette smoke and what is released from nerve tissue after stimulation of nicotinic receptors. Vleeming *et al.* (p. xxx) searched the literature from 1995 to 2001 to assemble the evidence against NO. They found that:

- NO inhaled in smoke immediately dilated airways and pulmonary blood vessels, allowing the smoke an

easier and deeper passage into the lungs, thus exposing the body and brain to increased nicotine and raising nicotine's addictive impact.

- Smoking decreased the concentration of exhaled NO as well as the concentration of NO metabolites in plasma, sputum cells, urine and nasal fluid. Smoking was associated with reduced synthesis of NO, which in turn was linked to high cholesterol levels, diabetes, hypertension, atherosclerosis, thrombosis and opiate addiction.
- Nicotine-induced release of NO in the brain acted both as a cerebral vasodilator and as a non-conventional neurotransmitter. It also appears to be associated with stress reduction by inhibiting dopamine reuptake, thereby indirectly enhancing receptor stimulation and, presumably, the rewarding effects of nicotine.

The enzyme nitric oxide synthase (NOS) metabolizes the amino acid group L-arginine to produce NO in our bodies. NOS inhibitors can thus reduce the symptoms of nicotine withdrawal, but further study is needed to measure NO and NOS brain activity to learn whether NOS or a low L-arginine diet can help smokers overcome withdrawal symptoms. What also awaits further study is whether reducing the NO content of cigarette smoke can reduce nicotine absorption and thereby weaken the drug's addictive kick.

Brief reports*Case study: can quitting raise blood pressure?*

Smoking acutely raises blood pressure (BP), but can quitting also cause it to rise? McEwen and West (p. xxx) reported on the case of a 41-year-old nurse who had smoked 25 cigarettes a day since she was 18. Her BP remained about 100/50, she said, until she quit smoking – twice. The first time, she used nicotine nasal spray for 5 months, then complained of breathlessness, sweating and of feeling 'hot'. Her BP had climbed to 150/80. She returned to smoking and 5 days later her BP was again 100/50.

She quit again as part of a trial using nicotine patches. Six weeks after she quit, her BP had climbed from 98/49 to 120/60, and she again reported feeling 'very hot' and experiencing 'severe sweating'. She discontinued the patch, but her symptoms persisted, and 4 weeks later her BP was 170/90. She started smoking again, and her BP returned to its earlier levels.

The phenomenon has been seen in at least one clinical trial, the authors reported, in which small but significant rises, from 123 to 126, were found in systolic (but not diastolic) BP among the 67 smokers who quit, but not the 19 who did not. The systolic BP of one of those who quit rose from 150 to 200, and that of three others rose from 120 to 150.

'We believe that the possibility of some smokers becoming hypertensive when they stop needs to be

examined further,' the authors write. 'In the meantime, clinicians and others involved in helping smokers to stop should be alert to the possibility. However, they should also be careful not to frighten patients back to smoking.'

Kids caught in school: recruits for quitting

More than one in four U.S. high-school students say they smoked cigarettes in the past 30 days, but getting them into cessation clinics is not easy. To collect data on potential cessation-program recruits, Riedel *et al.* (p. xxx) surveyed 110 adolescents who had been caught with cigarettes at 11 high schools. All had been referred to cessation programs in exchange for reduced punishment (21 of them declined but did agree to answer a short-form survey). Although smoking prevalence typically increases with rising grade levels, the number of students caught and referred *declined* with advancing grade level in this sample. Some telling results:

- About half said that their five best friends all smoked; three-fourths said that at least three best friends did.
- About two-thirds said they smoked daily, three-fourths of them 15 cigarettes a day or less. The mean age when they started smoking was a little over 12, but one in five said that they had started before age 11.
- One in four said that they had tried to quit once in the past year, and 44% said that they'd tried at least twice, but as the investigators note, social desirability may have biased them toward stating an interest in quitting.
- They often had used questionable quit strategies. For example, four-fifths did not avoid their smoking friends or family, and 44% did not get rid of their cigarettes or other smoking paraphernalia, both highly recommended strategies for quitting. One-third increased caffeine consumption, which is the opposite of what is advised, since caffeine metabolism slows significantly during smoking cessation.

The findings suggest three ways to help adolescents quit smoking: educating them about specific strategies, discussing how to deal with peer pressure and parental smoking, and offering parents cessation resources and information on how to support someone who is trying to quit.