Nicotine: abused substance and therapeutic agent

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Tobacco dependence is a complex phenomenon that is not fully understood. Nicotine is the main alkaloid in tobacco and the addictive compound of tobacco. It can improve both mood and cognitive functioning; these positive effects are strong reinforcements for smokers and contribute to their addiction. Opposite results also have been reported, however, and the effects of nicotine remain controversial. Recent epidemiological and empirical studies have indicated that smoking or nicotine or both may have protective effects against certain diseases. These findings have suggested that nicotine may be used as a therapeutic agent. However, because a variety of nicotinic cholinergic receptors are present in the brain, new agonist compounds may prove to be more effective than nicotine for therapeutic purposes. Studies are reviewed and the suggestion made that nicotine may prove useful as a tool to help us understand normal and pathological brain functioning.

La tabacomanie est un phénomène complexe que l'on ne comprend pas à fond. La nicotine est le principal alcaloïde du tabac et son élément toxicomanogène. Elle peut améliorer à la fois l'humeur et le fonctionnement cognitif. Ces effets positifs agissent comme un puissant élément de renforcement pour les fumeurs et contribuent à leur asservissement. On a toutefois signalé des résultats contraires et les effets de la nicotine demeurent controversés. De récentes études épidémiologiques et empiriques ont indiqué que le tabagisme ou la nicotine, ou les deux, peuvent protéger contre certaines maladies. Ces constatations laissent entendre que l'on peut utiliser la nicotine comme agent thérapeutique. Or, comme le cerveau contient toutes sortes de récepteurs cholinergiques nicotiniques, de nouveaux composés agonistes pourraient se révéler plus efficaces que la nicotine sur le plan thérapeutique. On examine les études et laisse entendre que la nicotine pourrait se révéler utile comme moyen de nous aider à comprendre le fonctionnement normal et pathologique du cerveau.

Since the work of Langley more than a century ago,[1] nicotine has become a very well studied compound. Interest in nicotine has recently been revived because tobacco dependence investigations have suggested its potential as a pharmacological tool and therapeutic agent. Although nicotine is addictive, the mechanisms underlying its addictive properties are not fully understood.[2] The putative reinforcing effects of nicotine include improved attention, learning and memory, but the opposite findings have also been reported. Interpreting these results is complicated because many of the studies conducted have had significant meth-

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odological weaknesses.[3-5] However, it is clear that the mood and cognitive performance of smokers who abstain from smoking are impaired, and that this impairment may be a factor in relapse.[6,7] Studies done on animals support the conclusion that nicotine withdrawal contributes to the smoking abstinence syndrome.[8] Research on the diversity of central nicotinic cholinergic receptors illustrates the complexity of the effect that nicotine has on neurotransmitters and highlights gaps in our understanding of the way these mechanisms operate.[9,10]

The ability of nicotine to regulate mood and improve cognitive functioning can act as a strong reinforcer of tobacco dependence.[3,11] Smoking is an efficient way to self-administer nicotine because smokers can control the dose of nicotine delivered to the brain on a puff-by-puff basis.[12-14] Hence, smokers can modify their nicotine intake to obtain a desired effect, such as sedation or stimulation, although these effects may be task-dependent.[5,15] Through this regulation, smokers can control their mood and cognitive functioning, most likely because they are directly modulating nicotine availability to the dopaminergic and cholinergic systems.[16-21] Indeed, chronic smoking has been shown recently to inhibit monoamine oxidase B (MAO-B) — suggesting that it has antidepressive effects.[22] Such observations have fostered new perspectives on the use of nicotine as a therapeutic agent, particularly for people with neurological and psychiatric diseases.[23,24] The goal of this review is to integrate different aspects of the effects of smoking and nicotine on central nervous system functioning and human behaviour. These effects have provided the rationale to assess the therapeutic properties of nicotine as well as its use as a tool to better understand normal cognitive functioning.

Nicotine and tobacco smoking

Nicotine is the main alkaloid found in tobacco — a weak base that is readily absorbed by membranes because of its lipophilic nature,[5,25] which is the main explanation for the large number of ways to use tobacco (smoking, chewing, licking, drinking and sniffing). Smoking is particularly addictive because nicotine is absorbed through the arterial (pulmonary) rather than the venous system. This means that nicotine reaches the brain in about 10 seconds, even more rapidly than it would via intravenous administration.[24,26] Since the likelihood that a substance will be abused depends on the time between administration and central reinforcement, tobacco smoking can easily become addictive.[27-29] However, smoking is a complex behaviour; smokers have fingertip control of the dose, on a puff-by-puff basis, such that nicotine intake depends on the number, volume, duration and depth of inhalation of the puffs, as well as the dilution of smoke with the ambient air.[30,31] Because of this complex administration process, it is impossible to reliably predict individual nicotine intake from the nicotine content of the tobacco, which is only approximated by the smoking-machine yields provided by the US Federal Trade Commission.[13]

Nicotine and addiction

The peripheral nicotinic cholinergic receptor has been characterized as a ligand-gated ion channel composed of 5 subunits (2α, 1ß, 1δ and 1γ), and information about the central nicotinic receptors continues to increase.[9,32] Neuronal nicotinic receptors are distributed widely in the brain and ganglia and are made up of α and ß subunits only. Eight neuronal genes for the α subunit (α_2–α_9) and 3 neuronal genes for the ß subunit ($ß_2$–$ß_4$) have been identified.[23,33] The distribution of subunits and their combinations vary considerably in the central nervous systems of different species.[9,34] Two main binding sites in the brain for nicotine have been described, 1 high-affinity site composed of an $\alpha_4ß_2$ combination ($2\alpha_4$ and $3ß_2$) and 1 low-affinity site probably composed of α_7 subunits (homo-oligomer) only.[35-37] The latter is antagonized by α-bungarotoxin (mecamylamine is the antagonist of the high-affinity site) and appears to be involved in developmental processes of the brain, such as pathfinding and synapse formation.[10,38] Nicotine binds to nicotinic receptors that are located both on cell bodies and at nerve terminals.[10,39,40] Na^+, K^+ and Ca^{++} ions can permeate nicotinic receptors. That Ca^{++} can permeate nicotinic receptors reinforces the notion that nicotine may play a role in modulating the release of neurotransmitters such as acetylcholine, norepinephrine, dopamine, serotonin, γ-aminobutyric acid (GABA) and glutamate through presynaptic nicotinic receptors.[10,40,41] The effects of nicotine on the dopaminergic system appear to be central to its reinforcing properties both in animals and humans.[21,42] Administering nicotine systemically to rats produces a locomotor stimulant effect that originates from dopaminergic

mechanisms and depends on the integrity of the mesolimbic projections. These effects disappear when dopaminergic neurons are affected by lesions.[2,16,17] Nicotinic receptors are present on the cell bodies of dopaminergic neurons from the ventral tegmental area, and on their endings in the nucleus accumbens. There is also evidence that the A10 neurons and those of the ventral tegmental area are implicated in the psychostimulant effects of nicotine. Additional findings suggest that the reinforcing properties of cocaine and nicotine may share some common neural substrates localized in the mesocorticolimbic dopamine system.[43] Dawe et al[44] assessed the effects of haloperidol on the nicotine intake, subjective measures of craving (withdrawal symptoms, positive or negative reinforcement) and smoking satisfaction of light to moderate smokers. Smokers who took haloperidol had a higher nicotine intake (based on increased blood nicotine levels) than those who took placebo, but no differences were found between the 2 conditions on any of the subjective measures. These results may indicate that the dopaminergic receptor blockade decreases the normal level of drug reward, which leads smokers to increase their nicotine intake to maintain their satisfaction.

Specific properties of nicotinic receptor tolerance help explain tobacco dependence. Because of the relatively short elimination half-life of nicotine (2 to 3 hours), blood nicotine levels accumulate after 6 to 8 hours of regular tobacco smoking and then plateau until the last cigarette of the day. Nicotine levels decrease sharply during the night and very little nicotine is present in the blood of smokers in the morning; acute tolerance develops during the day, when nicotine blood levels increase, and disappears with overnight abstinence.[25] The heart rate of people who smoke increases after the first few cigarettes of the day, but acute tolerance develops so that no effect is observed later in the day. In contrast, skin temperature reflects cutaneous vasoconstriction that is inversely related to the rise and decline of blood nicotine levels and demonstrates no evidence of tolerance.[45,46] Acute tolerance may be related to or even develop because of receptor desensitization: when nicotine binds to a nicotinic receptor, allosteric changes occur and the receptor becomes insensitive to nicotine for some time.[34,47] The chronic tolerance that results from repeated smoking has not been extensively studied and its contribution to dependence is poorly understood.[24] However, administering nicotine to rats produces an increase in the number of central nicotinic receptors. There is some evidence that a similar phenomenon occurs in smokers, since the number of nicotinic receptors in smokers is 50% greater than in nonsmokers.[48] This up-regulation is the opposite of what is usually observed in receptor pharmacology; chronic administration of an agonist normally yields down-regulation. Up-regulation in people who smoke might be the consequence of receptor desensitization, although there is no evidence to support this hypothesis.[23,34] Recent studies suggest that this up-regulation may involve not the synthesis of new receptors but a decrease in their turnover rate,[49,50] even though it is not known whether the reinforcing properties of nicotine are subject to either acute or chronic tolerance. If nicotine tolerance develops in this way, the transiently high levels of nicotine that result from each puff may partially overcome tolerance to produce a pharmacological effect. This may account for the addictive nature of tobacco smoking.[6,25,51]

Understanding tobacco dependence

Studies of performance have been used to assess the effects of smoking and of abstaining from tobacco. Most reports suggest that abstinence impairs performance in smokers and that smoking or administering nicotine restores performance levels.[6,52] A major methodological problem encountered is that nicotine effects have not been directly assessed because the vast majority of these studies have involved only abstinent smokers. Because abstinent smokers are more likely to suffer withdrawal symptoms, the improvement in performance after smoking tobacco may result from direct effects of nicotine or from a reduction in the withdrawal-induced performance deficit.[4,5,53] Moreover, although the effect of nicotine on performance is generally inferred, it has rarely been assessed directly by measuring blood nicotine levels. Most studies have manipulated the type or the number of cigarettes (low- versus high-nicotine delivery) — measures that do not reflect the variability of individual smoking behaviour or nicotine absorption.[6,13] In addition, few studies have included nonsmokers in the control group because of the concern about testing the effects of nicotine on nonsmokers. Nonsmokers, especially people who have never smoked, likely have a different constitution than smokers in terms of

nicotinic cholinergic receptors.[54,55] They may never become smokers because they do not respond strongly to nicotine.[55,56] Consequently, any performance differences between smokers and nonsmokers may stem from constitutional variations rather than from nicotine. Thus, it is difficult to draw firm conclusions about whether nicotine directly affects performance.

A comprehensive review of 101 studies concluded that the enhancing effect of nicotine on cognitive functioning is limited and likely does not influence whether a person starts smoking tobacco.[4] However, two recent studies that were unavailable when this review was conducted suggest that nicotine can directly affect nonsmokers. In the first,[57] event-related potentials (ERPs) were measured in order to monitor performance after nicotine was administered subcutaneously to people who had never smoked. They were asked to perform a visual-stimulus choice response-time (RT) task with 4 discriminate levels of difficulty. A double-blind procedure allowed the results of 3 groups to be compared: those who received an injection of nicotine, those who received an injection of a placebo (0.8 mL saline solution) and those who received no injection. Nicotine shortened P300 latency on only the most difficult level of the task. These results are similar to those of a previous auditory study[58] and suggest that nicotine facilitates stimulus evaluation performance on complex tasks. When the RT data were normalized by task condition and subjected to assessment of speed-accuracy trade-off functions,[59] nicotine increased the number of short responses without affecting the error rate. The performance of those who were administered nicotine improved, but the improvement was unlike similar RT effects for amphetamine, which also produced an increased error rate.[60]

More recently, a double-blind, placebo-controlled crossover study found that 2 subcutaneous doses of nicotine (0.3 and 0.6 mg) enhanced the performance of both smokers who had abstained from smoking for 24 hours and people who had never smoked.[61] Nicotine also shortened the RT in both groups of subjects engaged in a sustained attention task in which they were presented with a series of 100 digits per minute and instructed to press a button when they detected target sequences (defined as 3 consecutive odd or even digits). This replicates the findings of a similar study that used the same task but administered nicotine orally (in tablet form). In that study, smokers performed worse than people who had never smoked at baseline, likely because of withdrawal-induced impairment, but the performance-enhancing effect of nicotine was similar in both groups.[62] These findings indicate that nicotine has a direct effect on performance rather than merely relieving withdrawal symptoms, even though nicotine did not enhance performance of other tasks (finger tapping, memory scanning, logical reasoning, the Stroop test). One explanation is that the effect of nicotine on performance has an inverted U-shaped relation with plasma nicotine concentration in both smokers and nonsmokers.[63] When the large individual variations in blood nicotine concentrations from a given dose of nicotine are considered, an inverted U-shaped relation could account for the variability in the improvement of performance by both smokers and people who have never smoked.[57,61,64] Thus, these findings suggest that nicotine can be used by smokers to enhance cognitive functioning, although the mechanisms of tobacco dependence are complex and most likely involve both positive (performance enhancement) and negative (withdrawal relief) reinforcements.

Nicotine replacement therapy in smoking cessation

Nicotine has been recognized as the substance responsible for tobacco dependence,[6] and nicotine replacement therapy has been developed as a means to relieve this dependence. Nicotine replacement therapy is available as a gum, a transdermal patch, a nasal spray and an inhaler.[65,66] Although nicotine gum and patches have been shown to relieve withdrawal symptoms and improve abstinence rates,[23,67,68] the efficacy of these products may be limited by their pharmacokinetic profiles and by insufficient dosage.[69] Generally, people do not use enough gum during the day, and they chew it like regular gum. Because nicotine is absorbed slowly through the buccal mucosa and extensively metabolized by the liver when swallowed, the increase in nicotine blood levels after chewing nicotine gum is gradual, and only a small percentage of nicotine replacement is obtained.[65] The transdermal patch eliminates dosage and compliance problems by producing steady-state levels of nicotine. However, the percentage of nicotine replaced is an important issue; high doses are recommended for highly dependent smokers.[70] As of yet, the patch's slow release (4

to 6 hour peak) and passive administration does not respond to urges to smoke. The nasal spray is intended to treat highly dependent smokers, even though dosing and compliance problems may occur. Its pharmacokinetic profile, with a peak of 5 to 10 minutes, is similar to smoking, and the mechanism permits immediate self-administration in response to urges to smoke.[69] Nicotine gum and transdermal patches release nicotine slowly and produce much less reinforcement than smoking does, because tolerance develops as nicotine blood levels rise. In experienced smokers, nicotine nasal spray, which has a pharmacokinetic profile closer to tobacco smoking, does present some potential for abuse, but this risk is substantially lower than the risk associated with cigarettes.[65,71] The difference in the rate of nicotine absorption among these delivery systems may explain some of the cognitive deficits and mood perturbations observed when people try to quit smoking; the percentage of nicotine replacement may not be adequately tailored to the quitter's needs. Although nicotine replacement therapy has been demonstrated to be effective (Table 1), more research is needed to enhance long-term abstinence. One possibility may be to combine nicotine-replacement products, which has been shown to improve quitting rates.[67] Another is long-term follow-up with counselling.[72]

Nicotine as a therapeutic agent

Nicotine and Alzheimer's disease

The epidemiologic relationship between smoking and the occurrence of Alzheimer's disease has been clearly established since a review of 19 case–control studies and, more recently, a new case–control study have reported a significant negative association between the disease and smoking.[73,74]

Although cholinergic system integrity is necessary to produce good cognitive performance, most research on underlying mechanisms in cognitive performance has concerned the muscarinic cholinergic system.[20] Because scopolamine is a muscarinic antagonist and impairs performance in memory tasks, it has been used in animals to develop models of Alzheimer's disease. This has meant that the role of the nicotinic system in Alzheimer's disease has been overlooked. However, patients with Alzheimer's disease present large reductions of nicotinic receptors in both the neocortex and hippocampus compared with healthy people.[75–78] These results, and findings that nicotine has a positive effect on cognitive functioning in people without Alzheimer's disease, suggest that nicotinic receptors may contribute to normal cognitive functioning, and that patients with Alzheimer's disease may benefit from nicotine therapy.[78–81] The sustained visual-attention response time and perceptual performance of patients with Alzheimer's disease who were administered nicotine subcutaneously improved significantly in relation to the dose.[19] However, the nicotine did not affect performance in a short-term memory task, and global improvement was modest, although studies in animals suggest that chronic nicotine use, perhaps by inducing the up-regulation of nicotinic receptors, may increase cognitive functioning by stimulating a variety of neurotransmitters through presynaptic action.[20,23] Despite some promising results, long-term studies are needed to determine whether chronic nicotine use may provide sustained cognitive benefit.[82] An initial report has demonstrated that the cognitive functioning of 17 patients with dementia (vascular dementia, Alzheimer's disease and Parkinson's disease) improved after 2- or 4-week periods of nicotine administration.[83,84] Patients with dementia presented abnormal ERP latency, amplitude and electrical field, all of which improved after nicotine (22.5 to 52 mg per day) was administered. These results suggest that nicotine may enhance cognitive functioning in patients with dementia, and reinforce the idea that smokers may use nicotine for a similar purpose.

Table 1: Abstinence rates 1 year after smoking cessation in trials involving different nicotine replacement products[23]

Nicotine replacement product	Product or dosage received	Abstinence rate at 1 yr, %	Product or dosage received	Abstinence rate at 1 yr, %	Relative difference between groups, ratio
Gum	2 mg/stick	22	4 mg/stick	42	2.1
Transdermal patch	Placebo	10	Active product	19	2.2
Nasal spray	Placebo	11	Active product	26	2.3
Nicotine inhaler	Placebo	8	Active product	17	2.1

Mecamylamine is a nicotinic antagonist whose effects on performance have been assessed in nonsmokers.[85] The resulting impairment was similar to that observed in people in the early stages of Alzheimer's disease. Mecamylamine did not impair the recall of previously stored information but did impair the recall of newly acquired information. In a learning task in which subjects were asked to reproduce different response sequences (ranging from 1 to 10 button presses), the number of errors increased in relation to mecamylamine dose. However, when subjects were asked to reproduce the same sequence as fast as possible, mecamylamine had no effect on the number of errors. Similar results were found in a choice task, in which mecamylamine slowed response time. This result is similar to, but in the opposite direction of, the one reported in the previously mentioned study,[57] in which people who had never smoked received subcutaneous nicotine injections, which resulted in speeding of reaction time with no effect on the rate or type of errors.[57] The effect of mecamylamine on smokers and nonsmokers has also been tested through spontaneous electroencephalography (EEG) and performance.[86] For smokers and nonsmokers, the effects on EEG were similar, suggesting a direct pharmacological influence rather than an effect precipitated by nicotine withdrawal. Performance was impaired: response time on the vigilance and distractibility tasks were slower and delayed recall was impaired in a memory task. The authors concluded that nicotinic cholinergic mechanisms modulate the electrical activity of the brain and the cognitive functioning of smokers and nonsmokers, and that the disruption of these neural systems may mediate tobacco withdrawal symptoms and be involved in the pathophysiology of Alzheimer's disease. Since mecamylamine may also affect N-methyl-D-aspartate (NMDA) glutamatergic receptors, interactions between those agents cannot be ruled out, although the binding affinity of mecamylamine for these receptors seems to be about 9 times less than it is for nicotinic receptors.[20]

Another action of nicotine that may be related to Alzheimer's disease is neuroprotection. Most of the literature has focused on the neuroprotection of the dopaminergic neurons that may be implicated in Parkinson's disease; this is discussed below. However, recent data have shown that this nicotine effect may also be involved in the neurodegenerative process of Alzheimer's disease, and that nicotinic receptor stimulation may protect neurons against ß-amyloid toxicity.[87]

Future therapies may involve a cocktail of cholinesterase inhibitors and cholinergic agents, which would include nicotine. It could also involve specific muscarinic antagonists, since synergetic effects of muscarinic antagonists (atropine and M2 drugs) and nicotine have been shown to release cortical acetylcholine in concentrations up to 8 to 10 times higher than basal values, considerably more than simply the additive effect of muscarinic antagonist or nicotine alone.[88] The synthesis of new cholinergic agonists oriented toward specific receptor subtypes also might be an alternative. One such agonist (ABT-418) has already been tested on animals,[89–91] and human clinical trials are in progress.[24] Other agonists have been recently developed. RJR-2403 has a greater affinity for central receptors than peripheral ones,[92] and ABT-089 causes fewer adverse effects and has greater oral bioavailability than nicotine. ABT-089 has also been shown to improve cognitive performance in rats and monkeys and to exhibit neuroprotective properties.[93,94] The development of molecular research on neural nicotinic acetylcholine receptors and the recent development of novel nicotinic ligands are promising areas of research. Exploring various aspects of the nicotinic cholinergic system may increase our understanding of central nervous system functioning and the potential therapeutic use of nicotinic ligands.

Nicotine and Parkinson's disease

Epidemiological studies have demonstrated an inverse relation between smoking and the development of Parkinson's disease, with an odds ratio of about 0.5 for smokers compared with nonsmokers (smokers are half as likely to have Parkinson's disease).[95]

Studies on animals have indicated that nicotine stimulates dopamine release in striatal structures and in the substantia nigra, so that chronic nicotine administration increases motor stimulation. Such effects could be beneficial to patients with Parkinson's disease, in whom a deficit in dopaminergic function is found. Moreover, in the brains of rats, nicotine has been shown to protect nigrostriatal dopaminergic neurons from death induced by experimental lesions.[96–99] It has been suggested that the desensitization of dopaminergic neurons by nicotine may reduce Ca^{++} injury during acute lesions and consequently the

extent of cell damage or death.[100] This implies that, if nicotine therapy is to be used, it should be started when the disease is at an early stage. The first reported attempt to treat Parkinson's disease with nicotine involved subcutaneous injections of increasing doses over time.[101] Of 13 patients suffering from postencephalitic parkinsonism, 9 experienced improvement as a result of the nicotine injections — muscular rigidity lessened and facial expression and walking skills improved. Acute effects were evident but improvement did not last when treatment was stopped, and tremors were unaffected. More recently, the administration of nicotine was found to reduce tremors in patients with Parkinson's disease.[102] Nicotine administered transdermally has been tested in 2 patients, a former smoker and a person who never smoked.[103] Substantial clinical improvement was found, including a reduction of tremors, disorganized thinking and bradykinesia and a restoration of premorbid cognitive and motor functioning. Another study found that nicotine had only short-term effects in patients with Parkinson's disease, which reinforces the idea that, after increasing dosage, nicotine treatment should be maintained at constant level. Using a more controllable form to administer nicotine, such as gum or nasal spray, may be advantageous.[23,103,104] Although the possible interactions with traditional drugs used to treat patients with Parkinson's disease are unknown, combining nicotine or other nicotinic ligands with these drugs may reduce the effective dose of each and, therefore, reduce the adverse effects associated with each treatment when used alone.[23]

Nicotine and Tourette's syndrome

Gilles de la Tourette's syndrome is a genetic disorder that is thought to result from a basal ganglia abnormality and is typically treated with dopaminergic antagonists, such as the antipsychotic drug haloperidol. The rationale for administering nicotine to patients with Tourette's syndrome came from studies of animals in which nicotine significantly potentiated the hypoactivity induced by haloperidol, as assessed by the reduced cataleptic effects and locomotor activity.[105] The results from another study demonstrated that this effect was not observed when a selective D1 dopamine receptor antagonist (SCH 23390) was used, indicating that nicotine's potentiation of haloperidol-induced catalepsy was likely related to striatal D2 receptor mechanisms.[106] After the puzzling reports of patients with Tourette's syndrome whose symptoms (particularly tics) showed sustained improvement after acute administration of nicotine (via gum or transdermal patches), it appears that the pathophysiological basis of Tourette's syndrome may be an imbalance between cholinergic and dopaminergic activity within the striatum.[107–109] The relative inefficacy of cholinomimetic drugs (which act mainly on muscarinic receptors) and the importance of the nicotinic cholinergic system within the striatum suggest that nicotine could restore the cholinergic–dopaminergic balance by acting on nicotinic receptors, which in turn increase the activity of the GABAergic efferent striatal pathway on motor behaviour.[107] The dynamics of this return to normal balance, which is probably linked to the desensitization of nicotinic receptors, might explain why the observed clinical improvement may persist for days or weeks (between 8 and 16 weeks in this study) after acute (1 dose) or subchronic (6 days in this study) nicotine administration, although the elimination half-life of nicotine is relatively short (2 to 3 hours). Considering the many side effects induced by the neuroleptics used to treat patients with Tourette's syndrome, the potentiation of their effects by nicotine and the fact that a single patch may be effective for days suggest that the transdermal administration of nicotine could serve as an effective adjunct to neuroleptics in the treatment of Tourette's syndrome.[110]

Nicotine as self-medication

Table 2 reviews the positive effects of nicotine, which support its therapeutic use for purposes other than nicotine replacement therapy, as well as for self-medication. (Some effects may be directly related to nicotine dependence and may be sought by smokers.)

Depression

There is considerable evidence that tobacco smoking and depression are linked.[111,112] In a sample of 1200 young adults, nicotine dependence or smoking status was shown to be related to lifetime history of major depression. Of nicotine-dependent smokers, 26.7% had a history of major depression; of nondependent smokers, 12.0% had a history of major depression; and of nonsmokers, 9.4% had a history of major depression.[113]

There is a moderate to strong comorbity between depression and nicotine dependence in adolescents.[114] Teenagers with a depressive disorder had an odds ratio of nicotine dependence 4.6 times higher than that for teenagers without a depressive disorder. These findings suggest that the comorbidity between depression and nicotine dependence can be explained by common or correlated risk factors. Smoking is more prevalent in depressed people (46%) than in the general population (25%).[115] People who have had a major depressive episode have more difficulty stopping smoking, most likely because they suffer from a stronger withdrawal syndrome and have a greater risk of a depressive episode while they are trying to quit.[116–118] Although depressed mood was not listed as a symptom of smoking withdrawal in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R), it has been added in the fourth edition (DSM-IV).[7,119]

The monoaminergic theory of depression suggests that a reduction in norepinephrine or serotonin or both contributes to the affective, cognitive and behavioural deficits observed in the illness. However, dopaminergic depletion is involved at least in some aspects of major depression.[120] Studies on animals have found that dopaminergic systems are necessary to produce goal-seeking behaviour.[121] Lesions of the dopaminergic systems may modify this type of behaviour and may be particulary relevant to depression in humans, including the inability to experience pleasure (anhedonia) or a failure to seek out pleasurable events (emotional deficit). More recently, it has been argued that exposure to a single unavoidable or uncontrollable aversive experience leads to the inhibition of dopamine release in the nucleus accumbens and impairs the response to rewarding and aversive stimuli.[122] Restricting this approach to dopamine (although norepinephrine and serotonin may be involved and nicotine may also be used to stimulate their release), nicotine could stimulate dopamine release in mesolimbic structures, producing strong reinforcing effects for people exhibiting such emotional deficits.[123] Hence, smoking may be used by smokers as an antidepressant, since chronic smoking has been shown to inhibit MAO-B. MAO-B is involved in the breakdown of dopamine, which suggests that smoking tobacco produces some antidepressive effects.[22] Moreover, when the monoamine oxidase A (MAO-A) inhibitor, moclobemide, was used in a smoking cessation trial with some success, it was shown that tobacco smoking may also have some MAO-A inhibiting effects.[124,125] Although the serotonin reuptake inhibitor fluoxetine, administered for 10 weeks, has been shown to improve abstinence rates slightly (but not significantly) 9 months after smoking cessation,[126] a recent placebo-controlled study of bupropion, an antidepressant drug with a predominant dopaminergic profile, found that there was a significant dose-related effect on smoking cessation rates.[127] After 7 weeks of treatment, abstinence rates were 19.0% in the people who received placebo, 28.8% in the people who received 100 mg per day of bupropion, 38.6% in the people who received 150 mg per day of bupropion, and 44.2% in the people who received 300 mg per day of bupropion ($p < 0.001$). After 1 year, abstinence rates were respectively 12.4%, 19.6%, 22.9%, and 23.1%, with significant effects observed only for the groups that received 150 mg per day ($p = 0.02$) and 300 mg per day ($p = 0.01$). Given these outcomes, antidepressant drugs, particularly those with a dopaminergic profile of action, may become a useful

Table 2: The positive effects of nicotine in certain diseases (indicated with an x), which suggest a rationale for self-medication or therapeutic use

	Diseases on which nicotine has a positive effect				
Effect produced by nicotine	Alzheimer's disease	Parkinson's disease	Tourette's syndrome	Major depression	Schizophrenia
Enhances cognitive functioning	x	x		x	x
Provides neuroprotection	x	x			
Improves motor stimulation		x			
Potentiates neuroleptics			x		x
Reduces the side effects of neuroleptics			x		x
Regulates negative affect (anhedonia, blunted affect, lack of motivation)	x	x		x	x
Inhibits monoamine oxidase (unclear whether this is an effect of nicotine or of smoking)		x		x	

adjunct therapy for smoking cessation in heavy smokers who have a history of major depression, and are therefore at greater risk of depression after smoking cessation.

Nicotine and schizophrenia

Smoking is very prevalent among people with schizophrenia (around 90%), about twice as prevalent as among people with other psychiatric disorders, and 3 times as prevalent as in the general population.[115] People with schizophrenia are usually rated as heavy smokers and are usually highly dependent upon nicotine. Moreover, the history of heavy smoking in this population is usually related to early onset of the disease. The psychostimulant effects of nicotine might help these people compensate for their cognitive deficits, particularly attentional processes. It has been suggested that nicotine could normalize some of the neuronal deficits involved in the illness.[128] Adler et al[129] showed an impairment of sensory gating (measured by the P50 ERP component) in people with schizophrenia, and also found that smoking restored the impaired auditory information processing observed in people with schizophrenia who smoke. The normalization of the P50 component found after smoking in smokers with schizophrenia was not found in smokers who had no psychopathological disorder. A recent study has replicated these results in another group of people with schizophrenia.[130] As well, it has shown that the deficit levels of relatives of people with schizophrenia, who do not suffer from the disease, were between the levels for people with schizophrenia and those for people with no family history. Moreover, a linkage study found that this attentional deficit was associated with a mutation in a region of chromosome 15 corresponding to the site of the α_7 subunit involved in some nicotinic receptors.[131] A definitive relation cannot be fully assessed until the mutations responsible for the linkage are identified, but this result is important because it was already suspected that the α_7-nicotinic receptor is involved in the pathophysiology of schizophrenia. One hypothesis is that a deficient α_7-nicotinic receptor may impair normal brain development. When taken together, the effect of smoking on this sensory gating deficit and the possible involvement of the α_7-nicotinic receptor may explain the high prevalence of smoking among people with schizophrenia. Moreover, since nicotine has a lower affinity for the α_7-nicotinic receptor than for the more ubiquitous $\alpha_4\beta_2$-nicotinic receptor, people with schizophrenia may increase their nicotine intake to counteract these deficits, which in turn could explain why people with schizophrenia are usually classified as heavy smokers.[132,133]

People with schizophrenia may also use the effect of nicotine on mood to cope with anhedonia, or more generally to ameliorate negative symptoms.[111,134] Characteristics of negative symptoms, such as apathy and lack of motivation, may be related to the hypoactivity of the dopaminergic reward system, and, by stimulating the release of mesolimbic dopamine, nicotine may counteract negative symptoms.[111] Consistent with this view is the observation that the classic neuroleptic, haloperidol, induces increased nicotine intake in both both people with schizophrenia and normal smokers, whereas the atypical antipsychotic drug, clozapine, which, like nicotine, increases dopamine release in the nucleus accumbens, does not.[44,135,136]

People with schizophrenia may also use nicotine to lessen the side effects of neuroleptics (antiparkinsonian effects). This hypothesis is supported by the observed decrease in smoking and other substance use after treatment with clozapine — a drug that is associated with a lower incidence of extrapyramidal symptoms.[135,137] In nonsmokers treated with neuroleptics (except clozapine) or risperidone for a variety of psychotic disorders and reporting restlessness consistent with akathisia, nicotine transdermal administration (1 patch applied for 10 hours) was shown to reduce neuroleptic-induced akathisia.[138] It has been suggested that smokers experience fewer neuroleptic-induced extrapyramidal symptoms because smoking-related hepatic enzyme induction may lower their blood levels of neuroleptics. The results of the above study rule out this explanation, since the effects of nicotine on akathisia were assessed after only 10 hours' nicotine administration in nonsmokers.

Attentional deficit is obviously not restricted to people with schizophrenia. Some promising results have been obtained from the acute administration of nicotine to adults with attention deficit with hyperactivity disorder.[139] These data suggest that transdermal nicotine patches could serve as an effective adjunct to neuroleptics to treat people with schizophrenia, and that development of new nicotinic ligands may also help in our understanding and treatment of this disorder.

Nicotine as a research tool

Although the effects of nicotine on the central nervous system are not fully understood, they are contributing to a better understanding of neurotransmitter systems and some pathological states. Hence, more intensive study of the pharmacodynamics of nicotine is needed to better understand chronic nicotine tolerance. The characterization of smokers — both in terms of what they are seeking when they smoke and why they are smoking in terms of personality — is also a prerequisite.[3,140] The diversity of effects of nicotine, perhaps originating from the diversity of nicotinic receptors and their ubiquity in the central nervous system, may explain why it is so difficult to examine this behaviour. Reasons for smoking reported by smokers range from sedative to stimulant effects, and smokers may seek one of these effects more than the other.[141,142] Some personality traits may predispose individuals to the stimulating rather than the sedating effects of smoking. Personality dimensions such as sensation- or novelty-seeking behaviour and reward dependence may help us to better understand the motivation of smokers.[143,144] Novelty-seeking reflects behavioural activation and is considered to be a way to obtain reinforcement by activating dopaminergic systems. In animals, novelty-seeking and the susceptibility to self-administer substances of abuse seem to be linked.[145] The probability of becoming a smoker might be related to a person's ability to seek novel and rewarding behaviour. Individuals who are the most sensitive to the reinforcing properties of a drug may also be the most susceptible to dependence.[11,55] It can also be argued that negative symptoms (such as anhedonia or emotional deficit) are more likely to develop after smoking cessation among people who smoke for the stimulant effects of nicotine. The reverse is true for people who smoke for the sedative effects; they may become more anxious when quitting. Although understanding what motivates people to smoke will help us understand dependence, it may also help us to understand smoking withdrawal symptoms and provide information about therapeutic approaches. There is evidence that a synergistic effect of nicotine on the release of dopamine may have a strong positive effect on mood and cognitive functioning, and that smokers can regulate their mood using such reinforcing properties.[3,11,22]

The most recent research on nicotine has focused on its potential use as a therapeutic agent. The results of the clinical trials currently being conducted in different neurological and psychiatric diseases will be of great importance for future therapeutic use of nicotine as well as for the understanding of nicotine actions within the brain. Even if nicotine is not eventually used as a therapeutic agent in all the pathological conditions presented in this review, it could certainly become a useful tool with which to study normal and pathological brain functioning.

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