

Nicotine fix

Could the long-standing villain in tobacco yet prove a hero in medicine? Mounting evidence suggests that nicotine can help in certain diseases—but researchers are wary of giving cigarettes a good name. Apoorva Mandavilli reports.

Edward Sulzer began smoking when he was a teenager. He puffed his way through the army and continued to smoke when he became a professor of psychology at Southern Illinois University in Carbondale. In his late thirties, Sulzer developed lung cancer. After a year of hospitalization, at age 39, he died.

“You can see why I’m very anti-smoking,” says David Sulzer, who was 13 when his father passed away. But two weeks ago, Sulzer, now a neurobiologist at Columbia University, published a paper that in part explains how nicotine might benefit some people (*Nat. Neurosci.* 7, 581–582; 2004).

“I think there are a lot of drugs like that, that have some clinically beneficial effects,” says Sulzer, whose primary interest is in understanding how synapses work. “But the health risks of smoking far, far, far outweigh the benefits.”

Just as with the opiate morphine a few decades ago, nicotine is tapping into some uncomfortable contradictions in public health. On one side is the near-unanimous portrait of the drug as the addictive component of cigarettes. But evidence is slowly building that nicotine also has unmistakable positive effects in illnesses as diverse as schizophrenia, attention deficit and hyperactivity disorder (ADHD), Alzheimer and Parkinson diseases, ulcerative colitis and Tourette syndrome.

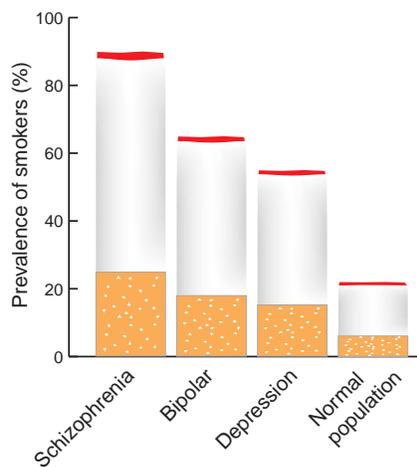
The debate on nicotine is further complicated because, unlike morphine, nicotine is available over the counter. Many scientists who study the drug’s beneficial effects are wary that their pro-nicotine comments may be distorted as pro-smoking by the media or by those with specific agendas. One researcher flat-out refused to grant an interview, and others were careful to word their comments in terms of nicotine-like compounds, rather than nicotine itself.

“Nicotine as a drug has some benefits. But if you ask me, ‘Is nicotine a good drug?’ No,” says Sherry Leonard, professor of psychiatry and pharmacology at the University of Colorado. “We just have to find [compounds] that do the same thing as nicotine.”

Where there's smoke...

Difficult as it may be to untangle the rewards of nicotine from the ravages of smoking, much of the evidence for nicotine’s benefits actually derives from epidemiological studies of the effects of smoking. For instance, smokers appear to have a lower risk of developing Alzheimer disease, Parkinson disease and ulcerative colitis.

In the 1960s, nearly half of the US population smoked cigarettes. That number is down to about 22%, a group that Yale University researcher Tony George calls “hard-core” smokers. Among the mentally ill, however, the proportion of smokers is much higher: up to 90% of schizophrenics, 70% of those with bipolar disorder and more than 50% of depressed individuals smoke. Some studies estimate that a third of those who smoke have at one time battled a mental illness. “Smoking is a marker for psycho pathology,” says George, who is director of the Program for Research in Smokers with Mental Illness at the Connecticut Mental Health Center. “What I like to say is, ‘Where there’s smoke, there’s fire.’”



Smoking gun: Large numbers of mentally ill smokers may be lighting up in an attempt to ‘self-medicate’ their symptoms.

Smokers often say that after a cigarette, their thinking is clearer, calmer and more focused. This effect is particularly prominent in those with a mental illness, such as schizophrenia or ADHD. “What we find is that nicotine and/or smoking seems to have positive effects,” says George. Many studies suggest that people with mental illness smoke because they are trying to ‘self-medicate’ and relieve the symptoms of their disorder, he says.

For instance, schizophrenics have trouble filtering important or ‘salient’ stimuli from unwanted noise. As a result, their brain is flooded with sensory overload, which could account for some of their paranoia and delusions. This ‘gating’ deficit is inherited, and about half of the first-degree relatives of schizophrenics have the same difficulty. Studies have shown that nicotine can normalize the ability to filter out noise in both schizophrenics and their first-degree relatives.

Depending on the type of incoming stimulus, dopamine neurons fire either at a slow ‘tonic’ rate or in rapid bursts. Most sensory inputs cause background or tonic firing, but certain salient stimuli come through as buzzes.

When people smoke or take nicotine in some other way, the nicotine binds to receptors in the brain, releasing dopamine and desensitizing the receptors. In that state, the receptors are no longer responsive to tonic signals. But high-frequency stimuli, such as food and sex, can override the desensitization and induce rapid firing. In essence, by filtering out extraneous noise, nicotine enhances the signal-to-noise ratio. “It cuts out nonsalient stimuli, so you experience it as a sharper phenomenon,” says Sulzer. “It’s not hard to imagine how that might help someone with delusions.” Low levels of methylphenidate (Ritalin) and amphetamines may do the same thing, Sulzer says.

Based on anecdotal and epidemiological information, researchers have also stumbled onto some unexpected effects of smoking, for example in preventing ulcerative colitis, a chronic, debilitating and largely incurable inflammation of the large intestine. Nonsmokers are five times more likely to develop the disorder than are current smokers; former smokers are at even greater risk.

There is some evidence to suggest that nicotine exerts a protective effect in the colon by inhibiting the production of interleukin-8 and other inflammatory cytokines. Nicotine may also enhance the production of a mucus layer between cells and the components of stool, and may have some effect on the nerves of the gut.

In patients with ulcerative colitis, 50% of those who began or resumed smoking after a flare-up went into remission. Patients who improved smoked twice as many cigarettes as patients who did not improve. Proof-of-concept studies suggest that delivering nicotine via transdermal patches can relieve ulcerative colitis symptoms, albeit with a lot of side effects (*Ann. Intern. Med.* 126, 364–371; 1997)

...there's fire

Despite its promise, developing nicotine as a treatment is fraught with pitfalls. Apart from its addictive nature and its action as a psycho-stimulant, nicotine influences the release of many neurotransmitters, including dopamine, GABA, glutamate and acetylcholine. "It's kind of a dirty drug because it does many, many things," says Edythe London, professor of psychiatry and pharmacology at the University of California in Los Angeles.

Addiction is primarily a concern only with cigarettes, which, by all accounts, are not an option for treatment. When people smoke,

there is a rapid rise in blood levels of nicotine, which corresponds to a spike in brain concentration, and then the levels fall off rapidly, rising again with the next cigarette. That sort of rapid cycling is what is thought to drive addiction.

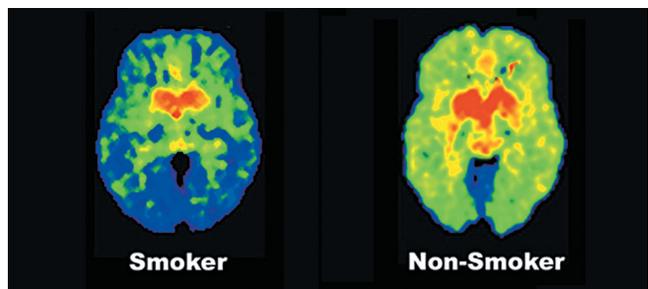
With the patch, peak blood levels are about 60% of those seen with smoking. Gradually increasing nicotine doses through the patch relieves symptoms, but evidence thus far suggests that it does not stimulate the central nervous system enough to become addictive. In nonsmokers, however, the patch is not well-tolerated and can have many side effects, including increased heart rate, lightheadedness, sweating and nausea. Blood levels with nicotine gum are even lower than with the patch, but chewing gum is too variable and difficult to monitor to be a viable treatment alternative.

"I'm not sure there's a hugely bright future for just the compound nicotine," says John Dani, professor of neuroscience at Baylor College of Medicine. "But I think there's a lot of potential for modifying the nicotinic system."

In the brain, nicotine binds to receptors of the neurotransmitter acetylcholine. Eleven subtypes of these nicotinic receptors—combinations of ten alpha and four beta subunits—have thus far been found throughout the central nervous system. Because there are several classes of receptors, levels of nicotine in the blood can have a wide variety of effects. Dani and others suggest that the receptors could be good targets for drug development. Understanding which receptor subtype is important in a specific disorder could help scientists design nicotine-like drugs that selectively bind to a specific subtype.

For instance, gene expression analysis has shown that in schizophrenics, nicotinic receptors, particularly the alpha-7 subtype, are expressed at lower levels. The gene for the alpha-7 receptor has also consistently been implicated in genetic studies of schizophrenia and, to a lesser extent, of bipolar disorder.

A clearer understanding of nicotine's therapeutic effects might also help combat addiction to it and other drugs. Although nicotine influences the release of many neurotransmitters, its effect on the dopamine system, which is important in reward-based learning, memory and addiction, has recently taken center stage. "We think that nicotinic receptors are an important part of the reward pathway," says Dan



Smoking reduces levels of monoamine oxidase, an enzyme that controls dopamine levels in the brain.

Courtesy of Brookhaven National Laboratory

McGehee, a neurobiologist at the University of Chicago. "If you block the receptors generally using an antagonist, you can maybe limit the rewarding effects of other drugs of abuse."

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As scientists unravel the components of the nicotinic system, it is increasingly clear that there are large holes in the understanding of the biology of nicotine, addiction, mental illness, stress—and how all of those things are tied together. "I don't want to say I'm not optimistic," says McGehee. "But there are many things we need to look at in more detail."

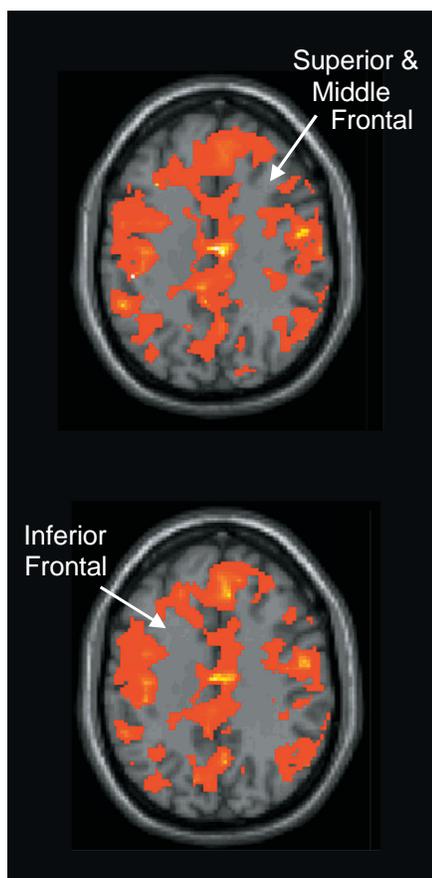
Until recently, for instance, clinical trials in schizophrenia often used nonsmokers as controls. Because most schizophrenics are smokers and nicotine has profound effects on the brain, including all combinations of participants might yield significantly different results.

The biggest challenge from a public health perspective, many researchers say, is that people might misinterpret evidence of nicotine's effects in certain disorders as an excuse to smoke or to not quit smoking.

On the contrary, in most people, nicotine might have harmful effects beyond those associated with smoking, says Sulzer. In people with schizophrenia, ADHD or other disorders where performance is suboptimal, nicotine raises the ability to filter stimuli to 'normal' levels. Except under extreme task demands, "normal people don't need this because their signal-to-noise ratio is already pretty good," Sulzer notes. In fact, several studies show that in healthy controls, nicotine either has no effect or, in some cases, can worsen performance.

But "if some idiot or drug company is going to twist things around," that important distinction might get lost, says Sulzer. "The only thing that would come out of [this research] that I'd be horrified by is if people used it to advocate smoking," he says. "I think it would be a real travesty if that happened."

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Edythe London, UCLA

When smokers abstain from cigarettes, there is greater blood flow as measured by fMRI—meaning their brains have to work harder—to perform the same working memory task.