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Great drug, shame about the delivery system

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Tobacco is bad for your health, but nicotine may be good for it

IT IS decades since cigarette companies advertised the health-giving properties of their products, but it has been suspected for some time that cigarettes, for all their harmful effects, serve to protect people against Parkinson's disease. Not only do smokers suffer less from Parkinson's than their abstemious counterparts, but those who do develop it frequently have a milder form. And Parkinson's is not the only illness that tobacco seems to help. Psychiatrists have observed for many years that cigarette smoking is almost ubiquitous among people with schizophrenia, leading to suggestions that this activity is a form of self-medication.

No one, of course, is suggesting that smoking is a healthy thing to do, even for those with Parkinson's or schizophrenia. But these observations have led researchers to experiment with more controlled doses of nicotine, the drug that makes smoking tobacco so desirable and addictive.

The results may surprise those who see the weed as an embodiment of evil, for those studies suggest that nicotine administered by injection or by a skin patch can alleviate the symptoms not only of Parkinson's disease, but also of Alzheimer's disease and Tourette's syndrome. All of which is leading to a more systematic investigation of nicotine as a treatment in its own right, and a search for similar molecules that have the same, or even enhanced, effects without suffering from the dreaded association with tobacco and all its ills.

Nicotine on the brain

Nicotine works by stimulating the production of a chemical called dopamine. This substance is a neurotransmitter—one of several dozen chemical messengers that carry signals from one nerve cell to another. The reason that smoking is fun is that dopamine is part of the nervous circuitry involved in the perception of pleasure.

Nicotine actually exerts its effect by mimicking a second neurotransmitter called acetylcholine. Dopamine-producing nerve cells have acetylcholine-receptor molecules on their surfaces. When these so-called nicotinic receptors are occupied by acetylcholine molecules, a cell is encouraged to churn out dopamine. Nicotine is sufficiently similar to acetylcholine for it to be able to lock into these receptors, artificially encouraging dopamine production.

Dopamine, however, has roles other than the generation of a feel-good factor. Both Parkinson's and Alzheimer's diseases, for example, are associated with a dopamine deficit. So attacking them with nicotine seems worth a try.

Pursuing this line of reasoning, Paul Newhouse, a psychiatrist at the University of Vermont, and his colleagues, have been administering the stuff to their Parkinson's and Alzheimer's patients. And they have, indeed, found that people with Parkinson's disease are better able to stand up, walk and resume sitting following the administration of nicotine. They also saw enhanced learning and memory skills in these patients and in a group of people with Alzheimer's disease that they tested.

All this has prompted drug companies to ask themselves if they can improve on nicotine (and, of course, produce a patentable product as opposed to a drug that anyone can sell). One such company, Abbott Laboratories, has already embarked on trials of a compound called ABT-418, which stimulates nicotinic receptors. Dr Newhouse and his colleagues have tested ABT-418 in a small number of patients with Parkinson's and Alzheimer's diseases, with promising results.

That, given the evidence from smokers, and the way that nicotine works, is encouraging, but not surprising. The unexpected finding is that nicotine also appears to help children with Tourette's syndrome—curious, given that this disease is caused not by a lack of dopamine, but by a surfeit.

Tourette's syndrome is marked by movements such as shoulder shrugging, eye blinking and head jerking, as well as bizarre vocal tics including barking and uncontrollable outbursts of profanity. Its sufferers are often treated with haloperidol, which blocks the receptor molecules that dopamine stimulates, but this drug does not work well in everyone and can have unpleasant side-effects.

Paul Sanberg, a neuroscientist at the University of South Florida in Tampa, and his colleagues, have found that a nicotine patch enhances the ability of haloperidol to suppress the symptoms of Tourette's. According to Dr Sanberg, the paradox of nicotine use in this case is explained because the drug is being administered continuously, via a patch, thus overloading the nicotinic receptors. Although the nicotine at first stimulates dopamine production, eventually the receptors become flooded with nicotine and shut down. Cigarettes, by contrast, deliver nicotine in small, short-lived jolts.

The patch is no panacea. At least 70% of the children tested developed extreme nausea from it. Nevertheless, Tourette's syndrome is so distressing to patients and their families that doctors who treat the disorder are getting more and more requests for nicotine patches. Indeed, in America, the Tourette Syndrome Association felt it necessary to issue a statement warning of the paucity of long-term safety data, especially in children, and the potential interactions of nicotine with drugs given to treat the syndrome.

But even though it has its problems, nicotine points the way to better treatments for Tourette's too. Dr Sanberg and his colleagues are currently testing one of those—a compound called mecamylamine. This was developed some years ago by Merck to treat high blood pressure, and it works by blocking nicotinic receptors on the nerve cells that control that pressure, thus preventing the release of dopamine. (Yet another of that neurotransmitter's roles is in the regulation of blood pressure.)

Mecamylamine can be taken in pill form and does not produce the nausea associated with a nicotine patch. When administered in a preliminary trial to 24 patients with Tourette's syndrome it provided significant relief to 22 of them.

In the meantime, says Dr Sanberg, people with Tourette's syndrome who have not responded to more conventional therapies have nothing to lose by asking their doctors to prescribe mecamylamine, perhaps to take in addition to their current medication. He also believes that further studies of the nicotinic receptor system in the brain could shed light on other psychiatric diseases, including schizophrenia, bipolar disorder and attention-deficit/hyperactivity disorder.

For these and other conditions, he says, nicotine and its relatives offer an alternative line of attack to that used by existing drugs. And there are, after all, few things more satisfying than converting an ancient enemy

into a bosom friend.

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