Effects of Withdrawal From Nicotine Versus Electronic Cigarette Fluid on Intracranial Self-Stimulation in Rats

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Abstract
Nicotine is known to create adverse withdrawal after dependence is gained. It is hypothesized that electronic cigarette fluid would cause even worse effects, as they contain undisclosed added constituents. The understanding of the other constituents effect on the withdrawal of the drug is important to further understand the addictive qualities of such constituents. Electronic cigarette fluids are not currently regulated by the FDA and electronic cigarette companies do not disclose what added constituents are present in their fluids. The aim of this study was to determine if the other constituents played a major role in tobacco dependence by observing the rats through intracranial self-stimulation (ICSS) threshold in rats by forcing dependence and then withdrawal symptoms onto the rats. This study did not show any major differences between pure nicotine and electronic cigarette fluids, leading to the conclusion that nicotine is the major component in addiction, as well as withdrawal from the drugs. The results do represent enough unknown factors that show that the drugs need to continue being studied in order to place more restrictions by the FDA.

Background
Nicotine has been shown to cause adverse withdrawal effects. The emergence of new products into the market, known commonly as e-cigs, or electronic cigarettes are not understood. The effects of these new drugs could be worse than traditional means of tobacco products.

The new products need to be further evaluated to lead to the regulation from the FDA. Currently, it is not known what additional constituents are added into electronic cigarette liquids, but it is important for these drugs to be regulated to ensure that the new products are not causing more adverse effects than disclosed.

This study seeks to get an understanding of the added constituents, and their role in the withdrawal effects of nicotine products. The new products are commonly used as a mean of quitting smoking, or an alternative, “safer”, means of smoking. Studies are needed to show the actual impact of electronic cigarettes.

Methods
Rats were trained in Intracranial Self-Stimulation (ICSS) procedure until thresholds were stable. They were then put on a 4 week infusion process, where they were constantly administered pure nicotine, electronic cigarette fluid, or saline at doses of 3.2mg/kg/day by osmotic mini-pump. The first week was to gain dependence to the drug and no additional drugs were given. During the next three weeks, mecamylamine, a nicotinic receptor antagonist, was given to each rat on Tuesday and Friday at random doses ranging from 0.3-3.0 mg/kg s.c injection, to produce precipitated withdrawal effects.

Results
Injection of mecamylamine at low to moderate doses showed a slight increase in the ICSS threshold in rats infused with both nicotine and e-fluids, and had no effect on the saline rats (Fig 1, 2 and 3).

At medium to high doses of mecamylamine, thresholds were significantly elevated in rats infused with nicotine and e-fluids. Mecamylamine did not affect rats infused with saline (Fig 1, 2 and 3).

Electronic cigarette fluids produced the same magnitude of threshold, or withdrawal effect at each dose of mecamylamine, with no notable differences.

Conclusions
The results show that electronic cigarette fluid produce similar withdrawal effects as nicotine alone in rats, as measured using ICSS. This leads to the conclusion that nicotine is the major product that causes addiction and adverse effects during withdrawal. The withdrawal effects show the need for product standards by the FDA to focus on nicotine.

The symptom of withdrawal studied is anhedonia, where higher amounts of electrical stimulation is needed to maintain responding. Future studies of withdrawal are needed to understand effects other than brain stimulation, such as hunger or physical activity or symptoms outside of anhedonia.

This data does not show that electronic cigarettes cause more adverse effects than that of pure nicotine. It is shown that all of the studied products show harmful causes and adverse effects, proving that electronic cigarettes would not be a better means to help quit smoking, as they cause similar addictive effects that result in similar withdrawal from the drug. These results indicate further study is needed.

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