

Abstract:

Historically stable, the incidence of inadvertent exposures to nicotine products has increased in recent years. Much of this increase may be attributable to the advent of electronic cigarettes. The dramatic increase in adverse exposures to electronic cigarettes and liquid nicotine products also portends new and considerable risk of potential nicotine toxicity, given the previously inconceivable high concentrations of nicotine in these products. Furthermore, this increased risk of toxicity is borne disproportionately by young children. Inadvertent exposures to electronic cigarettes and liquid nicotine, most commonly in children less than 6 years of age and primarily via ingestion, result more often in adverse clinical health effects compared to conventional cigarettes. Vomiting is common, although severe nicotine poisoning may result in airway compromise, seizures, obtundation, and the need for critical interventions.

Keywords:

nicotine; nicotine toxicity; nicotine poisoning; electronic cigarettes; e-cigarettes; liquid nicotine; e-liquid; electronic nicotine delivery systems (ENDS)

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The New Dangers of Electronic Cigarettes

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A pair of 22-month-old twin boys finds their mother's electronic cigarette refill cartridge on the living room coffee table. They each drink the berry-flavored liquid and are found shortly thereafter by their mother, crying and spitting up. Twin A rubs his eyes, which causes sudden intense pain and conjunctival redness. Twin B starts to convulse and drool. The children's mother calls the Poison Control Center, who advises her to bring them to the emergency department immediately.

At the hospital, twin A complains of "upset stomach," eye pain, and vomiting. He is mildly tachycardic, but has otherwise normal vital signs and an unremarkable physical exam. Laboratory and imaging studies are deferred. This patient is treated with ocular irrigation with tap water. He has gradual resolution of his symptoms and normalization of his vital signs, is able to drink juice, and is discharged from the emergency department.

Twin B is found to be obtunded and demonstrates myoclonic jerking movements. He is bradycardic and unable to control his copious oral secretions. He requires intubation, paralysis and sedation, and is admitted to the intensive care unit. This patient is able to be successfully extubated the following morning and is ultimately discharged in stable, neurologically intact condition.

INTRODUCTION

Electronic cigarettes are relatively new and increasingly popular. The liquid nicotine used in these devices has received particular attention within the health care community in recent years, both because of the growing popularity of electronic cigarettes, and because of their high nicotine concentrations and thus increased risk for potential toxicity. Children in particular are now at risk of exposure to nicotine at doses essentially inconceivable prior to the development of electronic cigarettes. Understanding the use patterns of electronic cigarettes, the pathophysiology of nicotine, the epidemiologic data of

inadvertent exposures, and adverse clinical effects from these products should prepare clinicians to better manage the acutely nicotine intoxicated patient.

HISTORY OF NICOTINE

The natural history of tobacco dates back millennia and is chronicled by innumerable reputed ethnomedicinal uses. Tobacco is cultivated from *Nicotiana tabacum*, which is native to the Americas and a member of the *Solanaceae* family that contains almost 2500 species, including potato (*Solanum tuberosum*), eggplant (*S. melongena*), tomato (*S. lycopersicum*), capsicum-containing peppers, belladonna (*Atropa belladonna*), jimsonweed (*Datura stramonium*) and several species of nightshade. Nicotine was first isolated from the *Nicotiana tabacum* plant in 1828 by German chemists Posselt and Reimann.¹

Tobacco was introduced to Europe in the 16th Century. The French ambassador to Portugal, Jean Nicot de Villemain, after whom *Nicotiana tabacum* is said to have been named, reportedly brought tobacco plants to Paris in 1560 and introduced snuff to Catherine de Medici for use in treatment of her headaches. Within a century, nearly half of European men were using tobacco daily.²

Consumption of tobacco continued to increase worldwide over the following 400 years. In the United States, per capita consumption of cigarettes among adults peaked in 1963, at 4345 cigarettes per person per year, or more than half a pack per person per day.³ Since the mid 1960s and into recent years, conventional cigarette consumption in the United States has declined; the Centers for Disease Control and Prevention reports that between 2005 and 2015, the proportion of US adults who smoke decreased from 20.9% to 15.1%. Nonetheless, an estimated 36.5 million US adults continue to use conventional cigarettes.⁴

Electronic cigarettes, which may also be known as e-cigarettes or electronic nicotine delivery systems (ENDS), were first developed in China in 2003 and introduced to the US market in 2007.⁵ These devices deliver an inhaled dose of nicotine vapor to the user from a reservoir filled with liquid nicotine, also known as e-liquid. This liquid nicotine is concentrated, and many users elect to refill these reservoirs themselves with diluted aliquots from very highly concentrated bulk supplies. E-cigarette proponents advocate their use for multiple reasons, including to minimize adverse health effects of smoking, as compared to conventional cigarettes, to minimize cravings or withdrawal symptoms, to save money, or as a cessation aid to help smokers quit.⁶

Between 2010 and 2013, awareness of electronic cigarettes among US adults increased from 40.9% to 79.7%. Use of electronic cigarettes also increased; in 2013, an estimated 36.5% of current smokers (15.8 million adults, up from 9.8% in 2010), 9.6% of former smokers (4.9 million adults, up from 2.5%), and 1.2% of never smokers (1.7 million adults) reported ever using e-cigarettes. Overall, the prevalence of current electronic cigarette use among US adults increased from 1.0% in 2010 to 2.6% in 2013.⁷

E-CIGARETTE REGULATION

Federal and state oversight of electronic cigarettes is complicated and fragmented, and maximum nicotine concentrations in e-cigarettes are to date neither well established nor well regulated. As such, there remains widespread commercial availability of electronic cigarette products, including nicotine e-liquid. A simple internet search yields hundreds of individual retailer websites, each selling e-cigarette devices and refill liquids. Some retail products are high in both concentration and quantity, such as a 20-L container of unflavored 100 mg/mL liquid nicotine available for \$1000 from myfreedomsmokes.com. Assuming high oral bioavailability of swallowed liquid nicotine, this single product is sold directly to consumers containing an ingestible nicotine equivalent of up to 2 million conventional cigarettes.

Further complicating the sale and use of concentrated nicotine refill liquid is its often inconsistent and unreliable packaging, with significantly errant estimates of nicotine concentration. Laboratory studies have found the actual nicotine content of some products to be up to several-fold higher than advertised.^{8,9}

NICOTINE PHYSIOLOGY AND PHARMACOKINETICS

The physiology and pathophysiology of nicotine is remarkably intricate and even today not fully understood. Nicotine is an alkaloid that generally stimulates the central nervous system and autonomic ganglia via multiple molecular and cellular mechanisms. When nicotine binds to nicotinic cholinergic receptors in central nervous system neurons, ligand-gated ion channels open causing post-synaptic cation influx.¹⁰ Depolarization of these neurons leads to central nervous stimulation and excitation. However, in excessive or prolonged exposure, such as with large doses, nicotine can have seemingly paradoxical parasympathetic

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