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Substitutability of nicotine alone and an electronic cigarette liquid using a concurrent choice assay in rats: A behavioral economic analysis

John R. Smethells[a,*], Andrew C. Harris[a,b,c], Danielle Burroughs[a], Steven R. Hursh[d,e], Mark G. LeSage[a,b,c]

[a] Minneapolis Medical Research Foundation, 914 S. 8th Street, Minneapolis, MN, United States
[b] Department of Medicine, University of Minnesota Medical School, 420 Delaware Street, SE, Minneapolis, MN, United States
[c] Department of Psychology, University of Minnesota, 75 E. River Road, Minneapolis, MN, United States
[d] Institutes for Behavior Resources, Inc., 2104 Maryland Avenue, Baltimore, MD, United States
[e] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 1800 Orleans Street, Baltimore, MD, United States

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ABSTRACT

Background: For the Food and Drug Administration to effectively regulate tobacco products, the contribution of non-nicotine tobacco constituents to the abuse liability of tobacco must be well understood. Our previous work compared the abuse liability of electronic cigarette refill liquids (EC liquids) and nicotine (Nic) alone when each was available in isolation and found no difference in abuse liability (i.e., demand elasticity). Another, and potentially more sensitive measure, would be to examine abuse liability in a choice context, which also provides a better model of the tobacco marketplace.

Methods: Demand elasticity for Nic alone and an EC liquid were measured when only one formulation was available (alone-price demand) and when both formulations were concurrently available (own-price demand), allowing an assessment of the degree to which each formulation served as a substitute (cross-price demand) when available at a low fixed-price.

Results: Own-price demand for both formulations were more elastic compared to alone-price demand, indicating that availability of a substitute increased demand elasticity. During concurrent access, consumption of the fixed-price formulation increased as the unit-price of the other formulation increased. The rate of increase was similar between formulations, indicating that they served as symmetrical substitutes.

Conclusion: The cross-price model reliably quantified the substitutability of both nicotine formulations and indicated that the direct CNS effects of non-nicotine constituents in EC liquid did not alter its abuse liability compared to Nic. These data highlight the sensitivity of this model and its potential utility for examining the relative abuse liability and substitutability of tobacco products.

1. Introduction

The 2009 Family Smoking Prevention and Tobacco Control Act charges the Food and Drug Administration (FDA) to regulate tobacco products, including regulating the levels of nicotine and other non-nicotine constituents in tobacco products (Hatsukami et al., 2013). Specifically, it requires the FDA Center for Tobacco Products (CTP) to evaluate new tobacco products that claim to have reduced abuse potential or, at most, an abuse potential that is *substantially equivalent* to existing products (Berman et al., 2015; Brennan et al., 2014). Animal models are vital for this purpose because they allow studies (e.g., those controlling for the sensory effects of constituents) that are difficult to accomplish in humans (Donny et al., 2012). Those that utilize state-of-the-art methods for assessing abuse liability in animal models may be the most useful to inform regulatory policy on tobacco products.

There are several methods to determine the relative abuse liability of drugs in rats. Most often researchers use low fixed-ratio (FR) schedules to compare rates of acquisition and/or the amount of responding maintained by intravenous self-administration across a range of doses (Ator and Griffiths, 2003; Banks and Negus, 2012). A more robust method is to examine the reinforcing efficacy of a drug by measuring responding on a progressive ratio schedule (Hodos, 1961), where the response requirement increases after each reinforcer delivery to determine a breakpoint or the highest response requirement the drug will maintain across an effective dose range (Stafford et al., 1998). Collectively, these approaches have been used to compare the relative abuse

* Corresponding author at: Minneapolis Medical Research Foundation7, 01 Park Avenue, Minneapolis, MN 55415, United States.
E-mail address: smet0011@umn.edu (J.R. Smethells).

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liability of a drug; drugs that engender quicker and/or more reliable acquisition of self-administration, maintain responding across a broader range of schedule requirements and produce higher breakpoints are considered to have greater abuse liability (Ator and Griffiths, 2003).

Behavioral economics (Hursh, 1984) provides an alternative model to assess abuse liability that combines several of these aforementioned measures under a unified theoretical construct (see a review Bickel et al., 2000). In the behavioral economic model, drug intake is measured across a range of FR values (e.g., FR 1, 3, 6, 9, 15, etc.) to produce a demand curve whereby drug consumption (mg/kg) is plotted as a function of unit price (FR/mg/kg). The demand curve allows several abuse liability factors to be collectively assessed, including demand intensity (i.e., the amount of consumption with relatively free access [e.g., an FR 1]), breakpoint (i.e., the unit price where zero consumption occurs) and demand elasticity (i.e., the rate at which drug consumption decreases with increases in its response requirement or unit price [FR/unit dose]). Of these measures, demand elasticity provides an overarching metric for the abuse liability of a drug since it captures how sensitive drug consumption is to an increase in unit price (Hursh et al., 2013; Hursh and Roma, 2016). Demand is considered inelastic if consumption of a drug decreases slowly in proportion to increases in unit price. If demand for one drug is more inelastic compared to another drug, it indicates that it has higher abuse liability or essential value (Hursh and Silberberg, 2008).

A primary concern in evaluating the relative abuse potential of products is the possible role of addiction-relevant non-nicotine constituents (Brennan et al., 2014). Several studies have recently examined the potential contribution of non-nicotine tobacco constituents to the abuse liability of tobacco products. Some non-nicotine constituents (i.e., nornicotine and acetaldehyde) have been shown to maintain self-administration in isolation or to enhance the reinforcing effects of nicotine, suggesting they might contribute to the abuse liability of tobacco products via their direct reinforcing effects (Bardo et al., 1999; Belluzzi et al., 2005; Hoffman and Evans, 2012). Consequently, some of these constituents (e.g., nornicotine, anabasine) have been added to the FDA CTP's list of Harmful or Potentially Harmful Constituents (HPHCs) in tobacco products, which are chemicals or chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to users or nonusers (CTP, 2014). HPHCs must be measured and reported for all tobacco products by industry to provide a basis for determining whether new products are substantially equivalent to or pose a reduced health risk compared to currently marketed products.

To determine if the abuse liability of products is enhanced by an interaction between nicotine non-nicotine constituents (both known and unknown), researchers have compared responding for Nic to extracts from smokeless tobacco, cigarette smoke, and electronic cigarettes refill liquids (EC liquids). In general, there have been mixed findings using traditional and behavioral economic models of abuse liability with some studies showing no difference between formulations (Brennan et al., 2015; LeSage et al., 2016a, 2016b) and others showing extracts have an increased abuse liability compared to Nic under some conditions (Brennan et al., 2013, 2015; Costello et al., 2014; Gellner et al., 2016). Several factors have been proposed to explain these discrepant findings, such as the relative differences in non-nicotine tobacco constituents present across different classes of products (combustible versus non-combustible) and the various methods used to prepare extracts from the tobacco products (Brennan et al., 2015). Another factor that may have played a role in these inconsistent results was that they were all examined in isolation and not under concurrent access, which more closely mimics the human tobacco marketplace. Previous animal research has shown that the reinforcing efficacy of drugs can appear similar under isolated conditions, but differ under concurrent access conditions (Wang et al., 2001; Ward et al., 2005). Indeed, the demand elasticity of drugs (e.g., cocaine, ethanol, PCP, remifentanil) are not static and depend upon the availability of other reinforcers (e.g., Wade-Galuska et al., 2007, 2011; Campbell and Carroll, 2000; Carroll et al., 1995).

In humans, previous behavioral economic research has also assessed how the availability of alternative reinforcers alters the abuse liability of regular nicotine-containing cigarettes (e.g., Shahan et al., 1999; Johnson and Bickel, 2003; Johnson et al., 2004). Shahan et al. (1999) compared self-administration of regular and denicotinized cigarettes across increasing unit prices (i.e., the response cost/puff). When self-administered individually, both cigarette types had similar demand elasticity, suggesting that they had equivalent reinforcing efficacy. However, when self-administered concurrently across equivalent prices, regular cigarettes were strongly preferred to denicotinized ones. In a follow-up study, Johnson et al. (2004) examined substitutability of these different cigarettes by providing denicotinized cigarettes at a consistently low price while the price of regular cigarettes was increased. They found that demand for regular cigarettes was more elastic when denicotinized cigarettes were concurrently available compared to when only regular cigarettes were available (i.e., own- vs. alone-price elasticity, respectively; see Hursh and Roma 2016 for a review), and those denicotinized cigarettes fully substituted for regular ones (i.e., their intake increased as consumption of regular cigarettes decreased) (see also Quisenberry et al., 2016). Collectively, these findings indicate that while nicotine is a primary determinant of preference between cigarettes in a choice context, other aspects (e.g., sensory or central nervous system (CNS) effects of non-nicotine tobacco constituents) may contribute to the reinforcing efficacy of cigarettes that is not apparent when only one cigarette type is available.

The present study is an initial attempt to isolate the effect of non-nicotine constituents on the reinforcing efficacy of an EC liquid within a concurrent choice situation. We expanded on our prior work (LeSage et al., 2016b) that assessed, in isolation, demand for nicotine alone and an EC liquid in rats. While no statistical differences in demand elasticity were found in that study, a trend toward greater demand elasticity for EC liquid was apparent. We hypothesized that concurrent access to these alternatives might provide a more sensitive measure to detect differences in reinforcer efficacy, as has been shown previously (see Wade-Galuska et al., 2007). The present study examined the alone-, own- and cross-price elasticity of nicotine and an EC liquid by assessing initial preference between the alternatives and then increasing the unit price of the preferred alternative by escalating the FR value. Differences between demand elasticity when the preferred alternative was the sole commodity (alone-price elasticity) and when the other alternative was concurrently available (own-price elasticity) at a low fixed-price were compared to determine the substitutability of these commodities.

2. Method

2.1. Animals

Male adult Holtzman rats (Harlan, Indianapolis, IN) weighing 300–350 g at arrival were individually housed with free access to water in a temperature- (22° C) and humidity-controlled colony room. Upon arrival, rats were provided free-access to show for one week and then were food restricted to 18 g/day. Protocols were approved by the Institutional Animal Care and Use Committee of the Minneapolis Medical Research Foundation and were in accordance with NIH guidelines set forth in the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011).

2.2. Apparatus

Drug self-administration chambers (Med-Associates, St. Albans, VT) were composed of aluminum and polycarbonate walls and a stainless-steel grid floor. The chamber had three response levers, each with a white stimulus light located directly above, and a house light mounted centrally at the top of the back panel to provide general illumination. The front panel contained two response levers, separated by a food