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Reinforcer Pathology: The Behavioral Economics of Abuse Liability Testing

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Introduction

Understanding the abuse liability of novel drugs is critical to understanding the risk these new compounds pose to society. Behavioral economics, the integration of psychology and economics, can be used to predict abuse liability of novel substances. Here we describe the behavioral economic concept of reinforcer pathology (1), and how it may predict use of novel drugs in existing drug users and initiation of use in the drug-naïve.

Reinforcer Pathology

Reinforcer pathology refers to the interaction between two processes: 1) excessive valuation of a drug or other preferred commodity and 2) excessive preference for immediate rewards (1). The first process, excessive valuation, is measured by both intensity and elasticity of demand (2). Intensity of demand refers to the amount of consumption of a particular commodity unrestricted by price. That is, the answer to the question, “How much of a commodity would you consume if the commodity was free?” Elasticity of demand refers to the proportional change in consumption of that commodity as a function of the proportional change in price (i.e., how quickly one devalues the commodity with increasing price). Higher intensity of demand and lower elasticity of demand represent greater valuation of a commodity. Stated another way, greater consumption of a commodity while it is free (i.e., intensity) and greater defense of consumption in the face of increasing prices (i.e., low elasticity) both represent greater demand for that commodity. A demand curve can be generated to graphically depict both intensity and elasticity where change in consumption is plotted as a function of price (3). Figure 1a demonstrates excessive valuation of alcohol, in

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which heavy drinkers exhibit greater intensity (i.e., greater consumption at the \$0 price) and lower elasticity of demand (i.e., consumption of drinks even at higher prices) for alcoholic beverages (3).

The second process, excessive preference for immediate rewards, is measured by delay discounting, a task that ascertains the extent of the decrease in value of a reinforcer as a function of the delay to its receipt. The resulting data typically form a hyperbolic function (1,4), where steeper functions indicate greater discounting of the delayed reinforcer. Figure 1b depicts results of a seminal study in which opioid-dependent participants showed steeper discounting of delayed money compared to demographically matched, non-opioid-dependent participants (5). This and subsequent studies show greater evidence of excessive preference in drug-dependent populations compared to controls (4). Importantly, high rates of delay discounting are considered a trans-disease process, as steep discounting is evident in multiple disorders such as pathological gambling, obesity, cigarette smoking, and abuse of cocaine and alcohol (4).

Application of Theory to Abuse Liability of a Novel Substance

Determinations of demand—Traditional measures of human abuse potential (HAP) testing have focused on subjective drug effects, likelihood of continued use, and drug discrimination, without attending to effects of drug price. However, measures of demand elasticity provide complementary measures of reinforcing value and empirically estimate consumption across a range of prices. Accumulating evidence indicates that estimates of demand for a preferred drug are associated with real-world frequency of use (e.g., cigarettes or alcoholic drinks per day) and other indices of addiction severity (2,3). These behavioral economic demand analyses have been executed using hypothetical, potentially real, and real rewards (2). Therefore, demand analyses can and should be used to examine relative (i.e., compared to other drugs) or absolute (i.e., compared to placebo) abuse liability of novel drugs. For example, upon introduction of a novel substance (e.g., a new synthetic cannabinoid), measures of demand (i.e., intensity and elasticity) for that novel substance, placebo, and its positive control could be examined in existing cannabis users to allow for behavioral economic assessment of relative abuse liability. Such estimates may direct regulation efforts (e.g., price or schedules of controlled substances) and identify individuals who may be at risk for early adoption of novel substance use. Likewise, varying doses of these substances could also be examined; however, modern demand models control for differences in drug dose or potency (for review, see 2), indicating that estimates of elasticity of demand are independent of these parameters.

Despite the utility of these approaches, ethical concerns limit exposing drug-naïve research participants to novel, potentially harmful, substances. Thus, recruitment efforts should be focused on recreational drug users. Alternatively, to avoid these ethical concerns measures of demand intensity or elasticity could be applied to the probability of initiation of use. Here, investigators could examine how the perception of novel compounds in the absence of direct experience affects the probability of use. For example, drug-naïve participants (e.g., non-smokers) could report the likelihood they would use a novel substance (e.g.,

e-cigarettes) across a range of prices, given some description of the subjective effects and/or participants' pre-existing perceptions of e-cigarettes.

Determination of discounting—Excessive preference for an immediate commodity is associated with high rates of non-adaptive health behaviors, including drug use and dependence. Specifically, high rates of delay discounting differentiate drug-dependent populations from controls (for example, see Figure 1b) and, like measures of demand, correlate with real-world frequency of use and other measures of addiction severity (4). Moreover, evidence suggests that drug users not only discount monetary rewards more steeply than controls, but also discount their preferred drug more steeply than money (5). Thus, based on extant discounting research, those individuals showing greater discounting, in general, and of their preferred drug, specifically, would be most likely to initiate use of a comparable novel substance. Moreover, even within those who initiate use, discounting may predict the frequency of use of that novel substance.

Pathways to Prediction—In the above sections, we discussed the relevance of each component process of reinforcer pathology in determining risk of novel substance use independently of one another. However, the *interaction* between these processes is how reinforcer pathology manifests. This interaction can be represented using a two-by-two matrix, (Figure 2), in which the quadrant that combines excessive valuation *and* excessive immediate preference indicates reinforcer pathology. In assessments of demand and delay discounting, those who fall in this quadrant (shaded red in Figure 2) are likely at the greatest risk for initiating use of novel substances. Conversely, those falling in the quadrant that combines low valuation and low immediate preference (shaded green in Figure 2) are at the lowest risk. Those falling in other quadrants are at moderate risk. In this way, we propose that the reinforcer pathology model is uniquely suited to predict novel substance use. Specifically, based on a collection of demand and delay discounting data from individuals within a specific population, a yardstick could be developed to assess the relative abuse liability of a novel drug and the likelihood that an individual will initiate use.

This approach, however, should be implemented with care, as cultural norms can confound the extent to which we define reinforcer pathology. For example, cigarette smoking and problem alcohol use is robustly associated with higher rates of delay discounting (4). However, smoking is more prevalent in eastern European and Chinese cultures compared to others (e.g., North American). Conversely, those who follow the tenets of Islam traditionally do not consume alcohol. In these cases, we may mis-predict an individual's risk for initiating use of a given novel substance because the influence of cultural norms contributes variance unaccounted for by the reinforcer pathology model. Therefore, the implementation of any yardstick to measure relative levels of demand and immediate preference must first consider cultural norms.

Conclusion

Through the concept of reinforcer pathology, behavioral economics provides a rich set of measures and concepts relevant to the assessment of abuse liability. These methods have both quantitative rigor and are easily administered. Here we have illustrated how these

methods and concepts can help identify individuals likely to abuse and initiate use of novel substances. Although behavioral economic methods have been used in addiction research for over 26 years, their application in abuse liability testing is only now maturing. Thus, more controlled observations are necessary to empirically test the concepts outlined above and permit greater clarity in their application.

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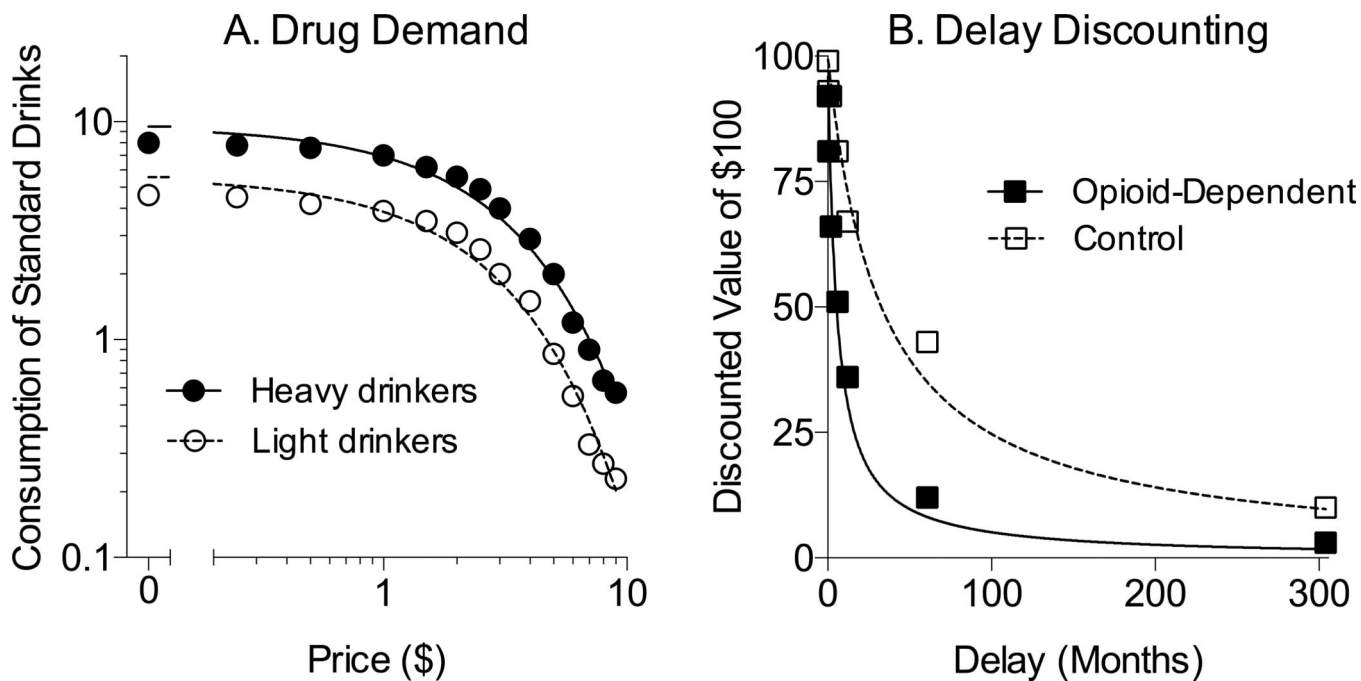


Figure 1: Measuring valuation and preference for the immediate using demand and delay discounting. (a) depicts valuation of alcoholic beverages over increasing prices in heavy and light drinkers. (b) represents the hyperbolic decrease in valuation of delayed money in heroin-dependent participants and controls. Data are replotted from (3) and (5), respectively.

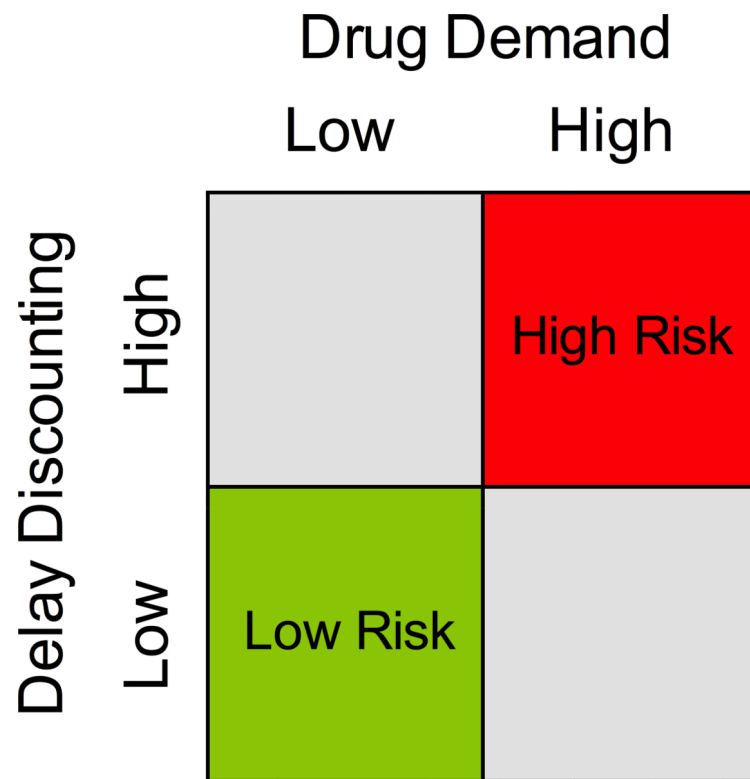


Figure 2:

Visual representation of the interaction between reinforcer value and an individual's preference for the immediate. The top right quadrant, depicted in red, represents the interaction of extreme valuation and excessive immediate preference leading to reinforcer pathology and sensitivity to abuse liability.