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LETTER TO THE EDITORS

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Nicotine may reinforce intravenous drug-taking behavior in drug users: reply to R. Dar and H. Frenk (2005)

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This letter is in reply to the letter of R. Dar and H. Frenk (2005), which criticized our paper, "Nicotine Serves as a Robust Reinforcer of Intravenous Drug-Taking Behavior in Human Cigarette Smokers" (Harvey et al. 2004). As described below, Dar and Frenk's criticism appears to flow from a misunderstanding of the methodology and a misrepresentation of our results.

One criticism is that the study used a small sample size. In fact, the sample size is typical for studies using a rigorous within-subject experimental design. Such a design is accepted as state-of-the-art by the US Food and Drug Administration, the Drug Enforcement Administration and the World Health Organization, as has been discussed elsewhere (Ator and Griffiths 2003; Balster and Bigelow 2003). Rather than depending on a large *N* "to give the principle of randomization, or simply randomness, a chance to 'work'" (Kerlinger 1973, p. 128), this design gains sensitivity by reducing between-group variability, allowing an effect to be observed with fewer subjects (Gliner et al. 2002). The fact that significant effects were clearly demonstrated in the study attests to the statistical power of the design as well as the strength of the effects.

Another criticism, which Dar and Frenk consider more important, relates to the subjects' history of occasional drug use prior to the study. Except for one subject who reported no history of illicit drug use, the research volunteers in our study were cigarette smokers who reported occasional use of an illicit drug over the past 10 years and, in five of eight subjects, recent use of alcohol and marijuana (within 2 weeks of the study). However, these subjects did not meet DSM-IV criteria (American Psychiatric Association 2000) for substance abuse or substance dependence for any drugs other than nicotine. Had they met these criteria for other drugs, they likely would have been placed in one of a number of treatment studies for cocaine or heroin dependence rather than the nicotine study. It is true that in our study the subjects' history of occasional drug use might make them different from a certain percentage of the general population who had never used alcohol or illicit drugs over the past 10 years. However, a large percentage of the US population has a history of using illicit drugs and alcohol. For example, in the 2002 National Survey on Drug Use and Health, 46% of individuals over the age of 12 reported lifetime use of any illicit drug and 40% reported lifetime use of marijuana (Substance Abuse and Mental Health Services Administration 2002). To this extent, a conservative interpretation of our results would still indicate that they are representative of a large portion of the population who have some history of occasional drug use, including alcohol and marijuana, but are not drug-dependent.

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It should be noted that the concern of Dar and Frenk with whether the subjects were drug users relates to the contentions that (1) "such participants [would] seek the psychoactive effects of nicotine," and (2) that "saline may be reinforcing in such participants." Regarding the first of these contentions, even if it were true that subjects with a history of occasional drug use would be more likely to sample a psychoactive substance, this self-administration would not be maintained unless the substance, by definition, served as a reinforcer. Regarding the second contention, although a propensity to self-administer placebo might make it difficult to demonstrate that nicotine is more reinforcing than saline in drug users, we fail to see how this argument applies to our study. As described below, the reinforcing effects of intravenous nicotine were clearly demonstrated in comparison to saline placebo in this study.

Dar and Frenk appear to have misrepresented our basic findings by stating that the study's "only significant finding" is that rates of responding and injections/session were higher for nicotine than saline at FR values at 200 and above. In fact, this was not the only significant finding. The lower panel of Fig. 1 (see Harvey et al. 2004) clearly indicates that subjects took significantly more nicotine injections than saline injections at FR values below 200, including FR 100 and FR10. At the lowest FR value, FR 10, all eight subjects took more nicotine injections than saline. Figure 2 further shows that, when data were collapsed across FR conditions, all three doses of nicotine were self-administered significantly more than saline and that self-administration of nicotine was dose dependent. Thus, nicotine clearly acted as a reinforcer over a range of doses and conditions. Perhaps the most elegant demonstration of these reinforcing effects is seen in the behavioral economics analysis presented in Fig. 3, where the demand for nicotine was seen to be inelastic (i.e., intake was defended) across the entire range of unit prices studied, a range which covers all FR values and nicotine dose levels.

In summary, we feel that our findings provide robust evidence that nicotine serves as an effective reinforcer of drug-taking behavior in nicotine-dependent human cigarette smokers and that smokers adjust their responding to maintain relatively constant levels of nicotine in the face of changing response requirements. Such compulsive behavior characterizes nicotine addiction and prevents millions of smokers from quitting successfully every year.

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