

## Letter to the Editor

## A Demonstration of Intravenous Nicotine Self-Administration in Humans?

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Sir

Sofuoglu *et al* (in press) recently reported a demonstration of self-administration of intravenous (i.v.) nicotine in male and female smokers. Given the recent controversy surrounding the addictive properties of nicotine in the absence of tobacco (eg Dar and Frenk, 2004), we read this article with great interest. In this study, participants completed three experimental sessions where they could choose to receive injections from two syringes beginning 15 min after sampling both. In each experimental session, one randomly assigned syringe contained saline and the other contained a randomly assigned dose of nicotine (0.1, 0.4, 0.7 mg). The authors reported a greater preference for the 0.4 and 0.7 mg doses of nicotine relative to saline and concluded that these findings demonstrate nicotine in the absence of tobacco is reinforcing to smokers. However, we believe that this conclusion may be premature.

A substantial body of evidence suggests that individuals' expectancies regarding a substance can significantly affect how they respond to it (eg Montcrieff *et al*, 2004). The expectancies and, in turn, responses can be influenced to the degree by which participants are able to distinguish between the active drug and placebo based on stimulus properties (eg Testa *et al*, 2006; Perkins *et al*, 2003; Greenberg and Fisher, 1994) as well as by *a priori* knowledge of what substances they may be receiving (eg de la Fuente-Fernandez *et al*, 2001; Mitchell *et al*, 1996). Evidence suggests that smokers are able to correctly distinguish between nicotine and inactive placebo on the basis of their subjective effects (eg Hughes *et al*, 1985) and that they will show an increased preference for a substance that they believe to be nicotine irrespective of whether or not they are actually receiving it (Hughes *et al*, 1989). It is therefore critical for participants to be adequately blinded

to the potential receipt of nicotine in order to adequately evaluate its reinforcing properties.

Unfortunately, the blinding procedures in the Sofuoglu study are not clearly reported. *A priori* knowledge by participants that they would be selecting between nicotine, a drug they may believe they are addicted to, and an inactive placebo would be expected to confound the results, especially if they were able to distinguish between the substances. This is a particularly important consideration given the robust subjective and physiological responses reported for the self-administered nicotine doses relative to placebo in the Sofuoglu study. Interestingly, in the only previous 'demonstration' of i.v. nicotine self-administration in humans, participants were explicitly informed that they would be responding for either nicotine or placebo (Harvey *et al*, 2004). Furthermore, numerous investigations that failed to observe nicotine self-administration have used protocols that have either attempted to blind participants to the substances they would be receiving (eg Henningfield *et al*, 1983) or to mask the stimulus properties of the placebo (eg Perkins *et al*, 1996).

We argue that until nicotine self-administration is demonstrated (and replicated) using paradigms that employ adequately blinded conditions, it is premature to conclude that nicotine has reinforcing properties in the absence of tobacco in humans.

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## DISCLOSURE/CONFLICT OF INTEREST

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financial holdings that could be perceived as constituting potential conflicts of interest.

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