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LETTER TO THE EDITORS

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Response to Dar and Frenk (2004), "Do smokers self-administer pure nicotine? A review of the evidence"

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This letter is in response to a recent review in this journal by Dar and Frenk (2004), which questioned the notion that humans self-administer "pure nicotine." [Actually, a more accurate term is "nicotine in novel forms, other than tobacco," because all nicotine products contain substances other than nicotine, and pure nicotine is lethal (Taylor 1990)]. The review focused on studies of nicotine nasal spray from our laboratory, as well as studies of intravenous nicotine and nicotine gum from other laboratories. It also generalized from this research on novel nicotine forms to question a "nicotine addiction" explanation for cigarette smoking.

In response, I will emphasize the following points: (1) robust self-administration of novel forms of nicotine by humans is demonstrated in research not included in the Dar and Frenk review, (2) they confuse procedures aimed at assessing changes in the relative reinforcing value of drugs with those intended to show absolute reinforcement, and (3) robust self-administration of novel forms of any drug usually requires extended drug access (e.g., beyond one session) so that individuals can adapt to unfamiliar effects and gauge the occurrence of desired effects. Although some of these points apply to all the studies reviewed by Dar and Frenk (2004), my focus will be on our nicotine nasal-spray studies.

First, as shown in Fig. 1, nicotine by nasal spray is robustly self-administered across days of access, relative to placebo-spray self-administration. In this study (Perkins et al. 1996a), smokers wanting to quit were randomly assigned to nicotine- and placebo-spray groups 1 day after quitting, and their self-administration behavior was carefully assessed over the subsequent 4 days. Both groups engaged in equal self-administration on the first day, but this behavior decreased sharply on subsequent days in the placebo group, perhaps reflecting extinction, while self-administration was maintained in the nicotine group (Fig. 1). This study was cited by Dar and Frenk (2004, p 24), not to address human nicotine self-administration, but, curiously, to support the "psychoactive and peripheral effects of nicotine."

Studies of more extended access to nicotine versus placebo gum (Gross and Stitzer 1989; Hughes 1998) and of nicotine versus placebo nasal spray (Nicotrol, Schneider et al. 1995) showed remarkably similar patterns of self-administration behavior, with comparable use between nicotine and placebo groups during the first week of access, followed by weeks and months of greater use by the nicotine group. This observation also supports point 3 above, the notion that novel drug forms often require extended duration of access in order to demonstrate robust self-administration. Ethical and practical concerns usually preclude studies of extended access to novel drug forms outside of clinical studies. Yet, Dar and Frenk excluded clinical studies from their review of the evidence. It is hard to understand how their rationale, smokers' "beliefs regarding the beneficial effects of 'nicotine replacement' (p 19), could explain persistently greater self-administration of a novel form of nicotine, versus placebo, that was not otherwise reinforcing. More recent, non-clinical research showed clear self-administration of nicotine by intravenous infusion (Harvey et al. 2004). Thus, evidence clearly shows that humans self-administer nicotine isolated from tobacco via nasal spray, gum, and intravenous infusion.

Second, Dar and Frenk (2004) misinterpreted measures of the relative reinforcing effects of drugs as indices of absolute reinforcement. Drug self-administration behavior is sensitive to the study procedures used, as well as other environmental contexts (Campbell and Carroll 2000), and measures of this behavior often have little meaning outside those contexts. In most of the studies from our lab that Dar and Frenk (2004) did review, self-administration was assessed using a procedure in which subjects engaged in repeated-choice opportunities between nicotine and place-

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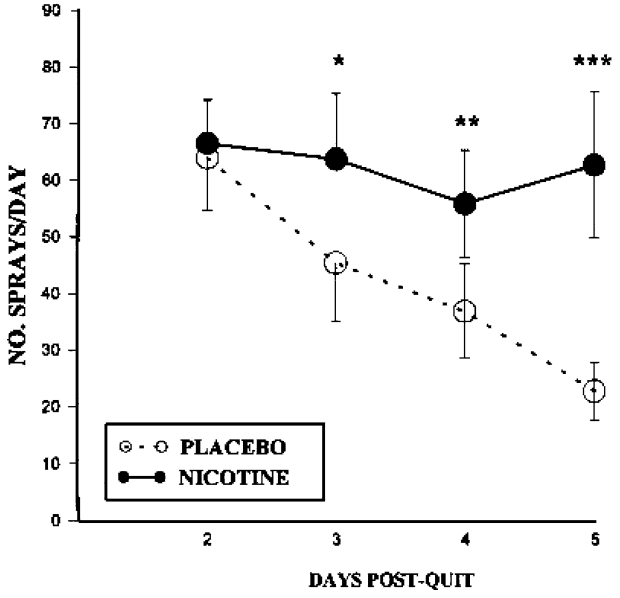

Fig. 1 Mean±SEM number of sprays self-administered across each of the four days of access (days 2–5 after quitting) by subjects in the nicotine (n=17) and placebo (n=18) groups who maintained continuous abstinence during the quit week. *P<0.05, **P<0.01, ***P<0.001 for differences between groups; from Perkins et al. (1996a). Reprinted with permission from the American Psychological Association

bo nasal spray (or cigarettes), following an initial exposure period to each spray. The objective of these studies was not to demonstrate the absolute reinforcing value of nasal-spray nicotine but to demonstrate differences or a change in the relative reinforcing value of nicotine (i.e., a shift in choice) as a function of smoking status or an acute manipulation of some kind, such as overnight smoking abstinence or pre-treatment with another drug. We purposely provided subjects with many drug choice opportunities in order to find each subject's drug choice level and avoid a "ceiling" effect. With this procedure, the number of nicotine choices was expected to be substantially less than the maximum, due to satiation and/or onset of aversive effects. While Dar and Frenk (2004, p 22) acknowledged that avoidance of "toxic levels" of nicotine could explain the moderate levels of nicotine-spray choice, they stated that we do not make that argument. We certainly did make that argument in the paper cited in that same paragraph of their review (Perkins et al. 1996b; see p 261), although we also considered evidence against this explanation.

Thus, the measure of self-administration emphasized by Dar and Frenk (2004), percentage of choices from the nicotine spray, will necessarily be a function of the total number of opportunities. The same number of nicotine choices will be greater than 50% of the total if fewer opportunities are provided or less than 50% if many opportunities are provided. We could have offered 100 or more opportunities and found no one who chose nicotine more than 50% of the time, or offered 10 or fewer opportunities and found that all chose nicotine more than 50% of the time. Therefore, choice of nicotine at or below 50% in these studies is largely a function of the high number of opportunities provided within a given period of time, due to the specific objectives of the research. As such, these studies of nicotine's relative reinforcing effects are not appropriate for evaluating the "absolute" reinforcing value of nicotine by nasal spray.

Third, self-administration of virtually any novel drug form by any species requires extended use to overcome lack of familiarity, including non-pharmacological sensory effects (Schneider et al. 1995), and to gauge its psychoactive effects via that form. Data from Perkins et al. (1996a; Fig. 1) suggests that at least a few days of access is needed for robust nicotine-spray self-administration in humans, none of whom in that study had prior experience with nasal-spray nicotine. As previously noted, another nicotine-spray product (Schneider et al. 1995) and nicotine gum (Gross and Stitzer 1989) also require extended access to show self-administration. These observations are not unique to human self-administration of nicotine via novel forms. Acquisition of self-administration of nicotine and many other drugs, such as cocaine, by non-human animals requires repeated access over days or longer (Campbell and Carroll 2000). Even cigarettes, which initially tend to have aversive effects, take many uses over months before humans begin to smoke on a regular basis (Eissenberg and Balster 2000). The same is true for alcohol and other drugs (Colder et al. 2002).

In their discussion, Dar and Frenk (2004) cited alcohol and cocaine studies using procedures similar to ours that showed greater choice for active drug versus placebo than those of our nasal-spray studies. They overlooked the fact that those studies used the same, familiar routes of administration as the abused products, unlike all of the nicotine studies they reviewed (intravenous, gum, and spray, rather than smoking). Moreover, Perkins et al. (1996b), cited in their review, conducted two studies examining choice of nicotine versus non-nicotine cigarettes, as well as nicotine versus placebo spray, each in abstinent and non-abstinent smokers. Choice of nicotine in both studies was greater after abstinence than non-abstinence, and overall choice of nicotine was lower via nasal spray than via cigarettes. Aside from showing that nicotine choice is sensitive to tobacco abstinence manipulations (the primary point of the paper), these observations suggest that drug choice is lower with an unfamiliar versus familiar form of administering the drug. The cigarette study also indicates that nicotine is critical to cigarette self-administration (as widely shown elsewhere; Rose and Corrigall 1997), counter to Dar and Frenk's questioning of the "nicotine addiction thesis (p 25)."

In summary, research ignored by Dar and Frenk (2004) does show robust human self-administration of nicotine in novel forms (i.e., isolated from tobacco), the general procedures of the nasal-spray studies reviewed by Dar and Frenk were aimed at showing changes in the relative reinforcing effects of nicotine by spray and not absolute reinforcing effects, and extended duration of access is necessary to show robust self-administration of any novel drug form. Finally, the fact that these studies, along with

an enormous volume of other research (Rose and Corrigall 1997), show that nicotine per se alters self-administration behavior is contrary to these authors' doubts about the importance of nicotine in tobacco dependence (p 18), doubts not shared even by the tobacco industry (Hurt and Robertson 1998).

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