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REVIEW

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Do smokers self-administer pure nicotine? A review of the evidence

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Abstract *Rationale:* Nicotine is almost universally believed to be the primary agent motivating tobacco smoking and the main impediment to cessation. A principal argument in support of the presumed reinforcing properties of nicotine is that smokers self-administer pure nicotine. However, the evidence for nicotine self-administration in smokers has not been critically examined. *Objectives:* To review and examine the empirical basis for the assertion that smokers self-administer pure nicotine. *Methods:* We reviewed all the studies we were able to locate that are cited as demonstrating self-administration of nicotine, isolated from tobacco, in normal smokers and non-smokers. These studies investigated self-administration of intravenous nicotine, nicotine gum and nicotine spray. Using the authors' own criteria, we examined whether these studies in fact demonstrate nicotine-self administration. *Results:* None of the studies we reviewed demonstrated nicotine self-administration in smokers. Both smokers and non-smokers failed to show preference for nicotine over placebo in any of these studies, including in a series of six reports of overnight abstinent smokers having access to nicotine nasal spray, a rapidly absorbed form of nicotine. *Conclusions:* The common statement that smokers self-administer pure nicotine lacks empirical support. Smokers in fact do not administer pure nicotine in any of the forms studied to date, even when abstinent and presumably nicotine-deprived. This conclusion necessitates a critical re-examination of the nicotine addiction thesis.

Keywords Nicotine · Self-administration · Dependence · Addiction · Smoking

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Introduction

Nicotine is commonly believed to be the primary agent motivating tobacco smoking and the main impediment to cessation (e.g. Stolerman and Jarvis 1995; Benowitz 1996, 1999; Rose 1996). Authorities such as the US Surgeon General (US Department of Health and Human Services 1988) and the British Royal College of Physicians (Tobacco Advisory Group of The Royal College of Physicians 2000) declared that nicotine is as addictive as heroin and cocaine. Countless research reports have reiterated this thesis in statements such as "Nicotine is the active ingredient in tobacco that leads to addiction" (Soria et al. 1996), "Nicotine can be viewed as a *primary* or *direct* reinforcer" (Kozlowski et al. 2001, p. 73, italics in original), or "The reinforcement provided by nicotine is a necessary component of the processes that drive smoking behavior" (Donny et al. 1998).

In the past decade, a substantial number of researchers have expressed reservations about the view that smoking is equivalent to nicotine addiction (e.g. Robinson and Pritchard 1992; Jacober et al. 1994; Warburton 1995; Gori 1996; Frenk and Dar 2000; Atrens 2001). Problems in the nicotine addiction account of smoking arise from a large variety of findings that appear to contradict it. These include, for example, nicotine's limited ability to induce self-administration in animals (McDonald et al. 1997; Dar and Frenk 2002), the failure of measures of dependence or withdrawal symptoms to predict smoking cessation (Kozlowski et al. 1994; Kenford et al. 2002), the limited efficacy of "nicotine replacement" devices for smoking abstinence (Balfour and Fagerstrom 1996; Silagy et al. 2003), the demonstration that denicotinized cigarettes are comparable with nicotine-containing cigarettes in terms of perceived reward and reduction of craving and withdrawal

(Shahan et al. 1999, 2001; Rose et al. 2000; Buchhalter et al. 2001), the lack of positive mood effects of pure nicotine even in abstinent smokers (Perkins et al. 1996b, Hughes et al. 2000a; West et al. 2000) and the absence of craving for nicotine or cigarettes in ex-smokers after wearing nicotine patches for 12 weeks as treatment for ulcerative colitis (Pullan et al. 1994).

While researchers are increasingly voicing the opinion that non-nicotine factors may be crucial in accounting for the ubiquity and persistence of smoking (Rose et al. 1993, 2000; Jacober et al. 1994; Shahan et al. 2001; Caggiula et al. 2002) and that the claims regarding the addictive properties of nicotine have been overstated (Warburton 1995; Gori 1996), most continue to maintain that nicotine is a powerful primary reinforcer and that its reinforcing properties are essential to smoking behavior.

A core argument in support of the thesis that nicotine is a primary reinforcer which motivates smoking is the claim that smokers self-administer pure nicotine. This argument was recently repeated in a study demonstrating the importance of environmental cues in nicotine self-administration and in smoking (Caggiula et al. 2001). While the authors emphasized the importance of non-nicotine factors in smoking, they reiterated the thesis that "nicotine is the primary constituent of tobacco that reinforces smoking behavior" (p. 516). One of their major arguments in support of this statement was that smokers self-administer pure nicotine: "Self administration of nicotine in isolation from tobacco smoke has been shown in smokers not trying to quit, using intravenous (Henningfield and Goldberg 1983), oral (Hughes et al. 2000a) and nasal (Perkins et al. 1996b) routes of administration" (Caggiula et al. 2001, p. 516). Essentially identical statements were made in other publications (e.g. Perkins et al. 2002).

The central role of this argument in the debate about the nicotine addiction thesis calls for a re-examination of the evidence for self-administration of pure nicotine in smokers. The present article reviews all the studies we were able to find through Medline searchers and by cross-references that examined self-administration of nicotine, isolated from tobacco, in smokers and non-smokers. We excluded from this review only studies in which nicotine was presented as a means to stop smoking, as self-administration in such studies is prone to reflect beliefs regarding the beneficial effects of "nicotine replacement" for smoking cessation. This problem was demonstrated in a series of studies with habitual smokers who declared a wish to quit smoking and agreed to abstain for the duration of the study (Hughes et al. 1985). In the first of three studies, participants were told that they would receive either nicotine or placebo gum. With these instructions, participants consistently self-administered the nicotine gum significantly more than the placebo gum. However, these experienced smokers demonstrated an excellent ability to distinguish between the gums, apparently on the basis of the nicotine gum's side-effects. Therefore, they may have preferred nicotine gum not because they liked its psychoactive effects, but rather because they believed it would be more helpful for them in overcoming craving. Two manipulations of expectancies were used to examine this possibility. In study 2, participants were told they would receive either the marketed nicotine gum or a new nicotine gum (which in fact was the same placebo) that was as effective as the marketed gum but had fewer side-effects. In study 3, participants were told to expect more side-effects from the placebo than from the nicotine gum. In both of these studies, participants self-administered equal amounts of placebo and nicotine gum. Thus, the instructions, and presumably the resultant expectations of the participants, controlled the extent to which nicotine was self-administered. Very similar results were reported in a later study by the same group (Hughes et al. 1989).

The studies we found investigated self-administration of intravenous nicotine, nicotine gum and nicotine spray. We begin by reviewing the widely cited studies of intravenous self-administration of nicotine by Henningfield and his colleagues and a more recent study by Rose and his colleagues. We continue with Hughes et al.'s studies of self-administration of nicotine gum, and conclude with the important series of studied by Perkins and his colleagues with nicotine nasal spray. For each of these studies, we attempt to determine whether or not it was able to establish self-administration of pure nicotine.

Self-administration of intravenous nicotine

We found six studies that examined self-administration of intravenous nicotine in humans. Only three of these, however, were published as journal articles (Henningfield and Goldberg 1983; Henningfield et al. 1983; Rose et al. 2003). The remaining three (Goldberg and Henningfield 1983, 1986; Swedberg et al. 1988) were published only as abstracts or book chapters and do not allow an evaluation of their methods and results. The first two studies (Henningfield and Goldberg 1983; Henningfield et al. 1983) were published in consecutive issues of *Pharmacology, Biochemistry and Behavior.*

The basic procedure of both studies was as follows: male cigarette smokers sat in a reclining chair for a varying number of 3-h sessions. They were prevented from smoking for 1 h prior to each session and during the session itself. An operant panel equipped with two levers was placed next to the chair. According to a preset schedule, pressing a number of times on one of the levers resulted in an intravenous injection of nicotine or saline; the other lever had no programmed consequences. Following each session, participants completed various questionnaires regarding their experience during the session.

Each of these studies reported results from only six participants, of which two (KU and KO) were included in both articles, so the total sample in both studies consisted of ten participants. Despite this small sample size, these two studies formed the basis for the Surgeon General's assertion that nicotine was reinforcing in humans (US Department of Health and Human Services 1988) and have been cited over 131 times (ISI Web of Knowledge) as

demonstrating nicotine self-administration in smokers. Therefore, although they have been critiqued extensively elsewhere (Robinson and Pritchard 1992; Frenk and Dar 2000), it is necessary to re-examine the validity of their conclusions in the context of this review.

The six participants in the first study (Henningfield et al. 1983) self-administered both nicotine and saline. The authors failed to report the complete data on the number of nicotine and saline injections self-administered by the participants. The partial data they do report, however, indicate that some of the participants administered at least as much saline as they did nicotine. One subject, for whom the number of injections is reported (SK), self-administered 22 saline injections, compared to only eight injections of nicotine at the 1.5 mg dose, five at the 0.75 mg dose and five at the 3.0 mg dose. These data do not provide evidence for nicotine self-administration; if anything, they suggest a preference for saline over nicotine.

Moreover, four of the six participants in this study "had histories of abuse of a variety of drugs, including opioids, stimulants and sedatives" (Henningfield et al. 1983, p. 887). There is considerable evidence that injection of saline, or even an injection ritual, may be reinforcing in such participants (Wen and Ho 1982; Powell 1995), hence little can be generalized from the behavior of participants with documented history of multiple drug abuse. Indeed, as the second study reports, in the two participants without a history of drug abuse, "nicotine suppressed self-administration rates to levels well below those maintained by saline" (Henningfield and Goldberg 1983, p. 1022).

After each session, participants were asked to identify the drugs they had self-administered. According to the authors, "All four subjects with histories of drug dependence (including cocaine abuse) identified the nicotine injections as cocaine" (Henningfield et al. 1983, p. 889). This is problematic from two respects. First, it is unclear how participants who were expressly informed that pressing the lever might result in nicotine injections could identify the drug as cocaine. Second, if the drug-experienced participants indeed identified nicotine as cocaine, then the findings concerning the pattern of nicotine administration by these participants are irrelevant for ordinary smokers.

In both studies, the authors justify their claim for nicotine self-administration by arguing that, while participants administered both nicotine and saline, "nicotine injections occurred in regular patterns whereas saline injections occurred with wide variability in pattern and frequency both within and across subjects" (Henningfield and Goldberg 1983, p. 1022). The only data provided to support this statement is a figure displaying the pattern of nicotine injections, and even this figure is incomplete: for three of the participants, it shows only a "representative session." The information on the pattern of saline injections, which is critical for comparison with the pattern of nicotine injections, is provided in a schematic drawing for only one of the participants with history of drug abuse. Furthermore, the authors claim that number of nicotine deliveries was inversely related to amount of drug per delivery. However, even in the two examples they select to support this statement, the number of injections does not convincingly imply an inverse relationship to dose: "For subject PE, number of deliveries were 25 at saline, 49 at 0.75 mg, 20 at 1.5 mg, and 10 at 3.0 mg nicotine per injection. In the third subject tested under such a procedure (S.K.), number of deliveries were 22 at saline, 5 at 0.75 mg, 8 at 1.5 mg, and 5 at 3.0 mg nicotine per injection" (Henningfield et al. 1983, p. 888).

The second study (Henningfield and Goldberg 1983) explored several variations of the previous procedure. Most variations were applied to only one or two participants. In one variation, three participants were faced with a pair of levers. Pressing the right lever produced a nicotine injection, as in the original procedure, whereas pressing the left lever blocked the next scheduled injection (injections were scheduled at 15- or 30-min intervals). Under these conditions, none of the three participants pressed the right lever. In addition, all three participants pressed the left lever to avoid some of the scheduled nicotine injections, and one of the three avoided 47 of 48 scheduled nicotine injections.

In summarizing this study, the authors acknowledged the lack of consistency in their findings: "In some of the subjects, nicotine maintained higher overall rates of lever-press responding than saline suggesting that nicotine was serving as a positive reinforcer. In other subjects, overall rates of responding during sessions, when nicotine was available, were lower than those when saline was available, suggesting that nicotine was serving as a punishing stimulus relative to saline" (Henningfield et al. 1983, p. 1022)." And later: "Clearly, the data are not consistent with descriptions of nicotine as consistently serving as a positive reinforcer or an aversive stimulus, or simply as a toxin lacking behavioral effects (p. 1025)." The results of these studies, therefore, do not appear to merit the conclusion drawn from them in the Surgeon General's report (US Department of Health and Human Services 1988), i.e. that they "demonstrated conclusively that nicotine itself can serve as an effective reinforcer in humans (p. 192)."

Recently, Rose et al. (2003) reported the results of a study designed to assess the effects of mecamylamine on nicotine self-administration in smokers. Smokers participated in two 4-h sessions in which they could self-administer intravenous nicotine ad lib in puff-sized bolus doses. Mecamylamine was shown to increase the rate of nicotine self-administration in these two sessions and to increase craving for cigarettes. However, the methodology of this study precludes any conclusions regarding nicotine reinforcement in smokers.

First and foremost, the criterion for drug self-administration in humans is typically defined as "self administration to a significantly greater extent than vehicle" (Perkins et al. 1997a, p. 239). Indeed, all other self-administration studies reviewed here did include a placebo control condition. Perhaps because Rose et al. (2003) did not aim to establish nicotine self-administration, but rather to

examine the effects of mecamylamine, they did not include a saline control. At any rate, self-administration of nicotine cannot be evaluated in the absence of any standard for comparison.

Second, the smokers in this study, despite overnight abstinence, did not self-administer nicotine spontaneously. As the authors report, "a pilot study suggested that participants required a training session before administering intravenous nicotine ad libitum, as they needed to be instructed that it would be necessary to press the response manipulandum several times within a 10-min period in order to maintain their usual rate of nicotine intake. In this [second] session, subjects were instructed to administer intravenous nicotine doses according to the same timing and number as they had taken puffs from cigarettes of their preferred brand during the first session (using an audible tone and visual cue to signal the time of each administration)" (Rose et al. 2003, p. 309). Thus, participants were expressly trained for 4 h to self-administer nicotine at a specific pace. While this procedure may be justified in order to establish a baseline for studying the effects of mecamylamine, it precludes any conclusions regarding the reinforcing properties of nicotine in this study.

Self-administration of nicotine gum

Following their study on the effect of instructions on the reinforcing effects of nicotine, cited above (Hughes et al. 1985), Hughes and his colleagues examined self-administration of nicotine gum in non-smokers, ex-smokers and current smokers in two pilot studies (Hughes et al. 1989). In the first, based on their earlier findings on the effect of instructions, the researchers did not inform the participants that the gums included either nicotine or placebo; instead, participants were told that the gums may contain a stimulant (nicotine was mentioned as one example), a tranquilizer, or a placebo. In reality, participants were given two packages of gum, marked as A and B, one containing nicotine gum and the other placebo gum. During a 9-h preference test, they were instructed to first chew one gum from each package, and then at least one more gum from either of the packages. As universally found in nicotine studies, both non- and ex-smokers strongly preferred the placebo gum. Among the current smokers, two preferred the nicotine gum, two had no preference and five preferred the placebo gum. Following their earlier findings (Hughes et al. 1985), study 2 aimed to examine whether nicotine would have served "as a more robust reinforcer" if participants knew they were receiving either nicotine or placebo. Study 2 replicated study 1 with current smokers only, who were now informed that gums A and B could both be nicotine gums, could both be placebo gum, or one could be nicotine and the other placebo. Under these instructions, five smokers preferred the nicotine gum, one had no preference, and three preferred the placebo gum—a non-significant difference.

A more recent study of self-administration of nicotine gum, which is cited by Caggiula et al. (2001) as demonstrating oral self-administration of nicotine in smokers, was undertaken by Hughes et al. (2000a). Nine former smokers (FS), 11 never-smokers (NS), and ten current smokers (CS) abstained from smoking for 16 h on each of 4 days. On each of 3 days, participants received three doses per day of 0, 2, or 4 mg nicotine gum in a randomized, double-blind, crossover design. Participants completed subjective effect scales before and after each dose. Three dependent measures were used to assess nicotine reinforcement. The first was simply asking participants whether they preferred gum A versus B, A versus C, B versus C, A versus no gum, B versus no gum and C versus no gum. The second was a form consisting of 60 choices that pitted gums A, B and C against receipt of money ranging from $0 to $10 in $0.50 increments. For each possibility, participants were required to circle whether they would rather receive a certain payment or three pieces of a certain gum when abstinent from smoking. The choices varied from choices in which participants indicated how much money it would require for them to forego receipt of three pieces of a certain gum (to quantify reinforcing effects) to choices in which participants indicated how much money it would require to motivate them to use three pieces of a certain gum (to quantify aversive effects). The third measure of nicotine reinforcement, which is the central one for this review, was voluntary self-administration. On day 4 (when abstinent from smoking), participants were given six pieces of gum A, six of gum B and six of gum C, and were told to chew as many of whichever gum they wished.

The results, in the authors' own words, showed that "active nicotine gum appeared to serve as a punisher in FS and NS smokers and a surprisingly mild reinforcer for CS" (Hughes et al. 2000, p. 260). Overall ratings of the nicotine gum were negative for all three groups, the only exception being that the abstaining current smokers rated the 2 mg gum as very slightly reinforcing. Specifically, using the number of dollars participants would be willing to pay for the gum, current smokers were willing to pay $1.1 for the 2 mg nicotine gum, while never- and former smokers were willing to pay up to $6 to not receive it. As for the 4 mg gum, even the 16-hour abstinent current smokers were willing to pay $2 to not receive it.

The self-administration data were entirely in accord with the above picture. Never smokers chose to chew, on average, 1.7 of the nicotine-free gum, 0.1 of the 2 mg nicotine gum and 0.3 of the 4 mg nicotine gum. For the former smokers, the corresponding numbers were 1.2, 0.2 and 0. Most importantly, the current smokers consumed on average 1.4 of the nicotine-free gum, 0.8 of the 2 mg nicotine gum and 0.3 of the 4 mg nicotine gum. Hence, even current smokers, after 16 h abstinence, chose nicotine only 42% of the time. Notably, the authors compared this percentage to 50%, which they present as chance level. However, there is no justification to lump the two nicotine gums together for the purpose of calculating probabilities. From the participants' point of view, the choice was between three gums (A, B and C), so the correct chance

probability for each gum is one third, making the chance probability of picking any nicotine gum 66.7%.

This error was corrected in a separate report on the same study (Hughes et al. 2000b), which presents the data of a fourth group, namely current smokers with a past history of alcoholism (PH). The results of these participants are compared to those of current smokers without such history (NH), which are the ten CS from Hughes et al. (2000a). Among PH participants, 83% of the gums chosen in the self-administration procedure contained nicotine, significantly more than the 42% chosen by the NH participants. This proportion was significantly larger than expected by chance (83 versus 67%), although the total amount of nicotine self-administered by the PH participants was not greater than expected by chance (7.9 versus 7.1 mg). Among NH participants, the total amount of nicotine self-administered was significantly less than expected by chance (2.8 versus 5.0 mg). According to Hughes et al. (2000b), "This measure also showed a non-significant trend for the proportion of gums that were nicotine to be less than chance (42 versus 67%, P=0.09)" (p. 1636). Note, however, that the difference between these proportions is actually larger than in the PH sample, and its failure to reach statistical significance is due to the smaller sample size in the NH group (n=10) relative to the PH group (n=20).

In summary, the results of this study do not support the assertion that smokers self-administer pure nicotine. With the exception of smokers with a history of alcoholism (of whom 45% also had history of other psychiatric diagnoses), participants did not self-administer nicotine in this study and did not find it reinforcing. In fact, nicotine in the form of gum appears to have been aversive not only to non-smokers and former smokers but also to abstinent current smokers.

Studies of nicotine nasal spray

Nicotine in nasal spray has the advantage that it presents measured doses of nicotine in rapid bolus form, similar to cigarette smoking (Perkins et al. 1994b). This is important, as according to the nicotine delivery kinetics thesis (Henningfield and Keenan 1993), the presumed reinforcing effects of nicotine depend on its speed of delivery to the brain. Therefore, a lack of nicotine reinforcement with slower delivery devices, such as the patch or the gum, may not be perceived as an insurmountable challenge to the nicotine addiction thesis. In contrast, as nasal spray provides rapid nicotine delivery, it should clearly be reinforcing to smokers under the nicotine addiction thesis, particularly following abstinence. This rationale was the basis for a series of studies by Perkins and his colleagues, which examined self-administration of nicotine nasal spray in smokers.

The first study of the series (Perkins et al. 1996b) is the one cited by Caggiula et al. (2001) as demonstrating nicotine self-administration, and its basic methodology was adopted in several later studies (reviewed below). Twenty-four smokers who were not interested in quitting were presented with two bottles of nasal spray. One colored bottle of nasal spray contained nicotine solution (1.5 μg/kg per spray). The nicotine dose per spray (0.1 mg for average weight subject) was designed to be comparable to the amount of nicotine in a single puff of cigarette. The spray delivered the designated amount of nicotine in saline, along with peppermint flavoring oil to disguise the taste and smell of nicotine. The other bottle, of a different color, contained a placebo solution that, in addition to the peppermint oil, included pepper extract to control for the sensory effects of nicotine.

Participants were first asked to self-administer six sprays from each bottle, with a 15-min rest between bottles. Subsequently, they were instructed to self-administer a total of six sprays from either or both bottles within a 3-min period. This forced choice procedure was repeated 8 times within a 2-h period, resulting in a total of 48 choice trials. Each participant went through the procedure twice: once following overnight smoking abstinence and once following no abstinence

The criterion for drug self-administration in this study and in those that follow, as defined by the authors elsewhere, was "self administration to a significantly greater extent than vehicle" (Perkins et al. 1997a, p. 239). With this definition, neither this study nor any of the subsequent ones, reviewed below, demonstrated nicotine self-administration. Under the abstinence condition, participants in this study chose to self-administer nicotine 47% of the times, just below chance levels, with only nine of the 24 subjects choosing the nicotine over the placebo spray over 50% of the times. Under the no abstinence condition, participants self-administered nicotine only 34% of the time—significantly lower than chance. In this condition, only three of the 24 subjects chose nicotine over 50% of the times. As the authors themselves acknowledged, this pattern suggests that nicotine was aversive to the non-abstinent smokers. Moreover, using the same criterion of choice of nicotine versus placebo spray, nicotine was at best neutral even for overnight abstinent smokers.

It could be argued, with hindsight, that the authors' criterion for nicotine self-administration was too stringent, as administering more nicotine than placebo in this forced choice procedure might constitute an overdose. According to this hypothetical argument (which the authors do not make), smokers may reach the desired blood level of nicotine after few administrations of nicotine, and thereafter select placebo sprays in order to avoid reaching toxic levels of nicotine. If this were the case, however, the nicotine-deprived smokers would be expected to self-administer more nicotine than placebo in the initial trials, gradually opting for more placebo than nicotine in later trials. However, a figure that depicts nicotine and placebo choices across trials (Perkins et al. 1996b, Fig. 1, p. 259) shows that this was not the case. Nicotine choices did not exceed placebo choices even in the very first trial following overnight abstinence, and there was no trend toward fewer nicotine choices in later trials. Therefore, the

results of this study can unequivocally be interpreted as demonstrating that nicotine in nasal spray was neutral for abstinent smokers and aversive for non-abstinent smokers.

A subsequent study by this group (Perkins et al. 1997b) employed the same procedure of 48 forced choices between nicotine and placebo spray. Participants were 11 smokers and ten never-smokers. Perhaps due to the results of the previous study, only the overnight abstinence condition was used in this and in subsequent studies (see Table 1). The results of this study were even less supportive of nicotine self-administration in smokers: The abstinent smokers chose nicotine only 36% of the time (mean of 17.5 out of 48 choices), with only three of the 11 smokers exceeding the no preference level of 24 nicotine choices. Never-smokers, as would be expected, chose nicotine less than 10% of the time (4.6 out of 48 choices).

Perkins et al. (1999) repeated the same procedure in a study designed to test the effects of mecamylamine and trimethaphan on various parameters, including nicotine self-administration. Again following overnight abstinence, the six smokers who participated in this forced choice procedure chose nicotine over placebo 15.8 out of 48 times when they did not received any drug (trimethaphan was supposed to be administered on that trial but was not, for technical reasons) and 14.8 out of 48 times when receiving placebo. Under mecamylamine, which was expected to block the effects of nicotine, the choice of nicotine spray over placebo rose to 21.3 times out of 48. These results indicate that nicotine was aversive to smokers in this study—again despite overnight abstinence—and that this aversion was neutralized by the blockade of nicotine receptors with mecamylamine.

In Perkins et al. (2001a), participants were 17 ex-smokers, 19 non-smokers, 45 dependent smokers and 12 non-dependent smokers, as determined by DSM-IV Tobacco Dependence criteria. While data are not reported numerically in this article, the figure depicting choice levels (Fig. 1, p. 246) shows that all groups chose nicotine over placebo less than 50% of the time, despite overnight abstinence (see Table 1). Notably, dependent smokers tended to administer less nicotine than did the non-dependent smokers. Moreover, ex-smokers did not differ from never smokers, both showing clear aversion to nicotine by preferring placebo to nicotine spray by a ratio of at least 3:1.

Fifteen dependent smokers participated in another nasal spray study (Perkins et al. 2001b) that included a forced-choice self-administration session following overnight abstinence. Prior to the self-administration procedure, participants were pretreated with a placebo, a moderate dose or a high dose transdermal nicotine patch. As in the other studies, the choice of nicotine over placebo spray never exceeded 50%, regardless of the experimental condition (see Table 1). Finally, 26 smokers wishing to quit participated in the most recent study by this group to use the forced choice procedure, again following overnight abstinence (Perkins et al. 2002). In this study, participants chose the nicotine spray over placebo an average of 23.7 times out of 48, i.e. at chance levels.

Table 1 summarized the results of all the nicotine nasal spray studies using the forced choice procedure. As can be seen in this table, none of these studies demonstrated nicotine self-administration according to the authors' own criterion. Specifically, even smokers who were presumably nicotine deprived did not prefer nicotine to placebo spray in any of these forced-choice self-administration studies.

Another study by the same group (Perkins et al. 1997a) employed a different procedure. Ten smokers who

Table 1 Summary of forced-choice self-administration results from Perkins et al.'s nicotine nasal spray studies

Study	Participants	Manipulation	% Nicotine choices (out of total choices)
Perkins et al. (1996b)	24 smokers	No abstinence	34
		Abstinence	47
Perkins et al. (1997b)	11 smokers	Abstinence	36
	10 never smokers	Abstinence	10
Perkins et al. (1999)	6 smokers	Abstinence	33
		Abstinence+placebo	31
		Abstinence+mecamylamine	44
Perkins et al. (2001a)	45 dependent smokers	Abstinence	46[a]
	12 non-dependent smokers	Abstinence	50[a]
	17 ex-smokers	Abstinence	25[a]
	19 non-smokers	Abstinence	19[a]
Perkins et al. (2001b)	15 dependent smokers	Abstinence+placebo	40[b]
		Abstinence+moderate dose nicotine patch	37[b]
		Abstinence+high dose nicotine patch	30[b]
Perkins et al. (2002)	26 smokers wishing to quit	Abstinence	49

[a]Numbers not provided, but determined from figure

[b]Numbers not provided, but determined from figure; male and female data aggregated

expressed a desire to quit participated in five sessions, each following overnight abstinence. In three of the sessions, they could sample ad libitum 0 (placebo), 0.75 or 1.5 μg/kg/spray nicotine sprays, with only one of these available per session. The fourth session involved ad libitum smoking. The order of these four sessions (three spray sessions, one smoking session) was counterbalanced among participants. In the fifth and final "free choice" session, participants were first exposed to six sprays of each of the three sprays they had sampled in the earlier sessions, and then instructed to administer as much as they wished of any of these sprays in the next 3 h.

During the sampling sessions, participants self-administered a mean of 47.6, 34.7, and 31.0 sprays of placebo, very low (0.75 μg/kg per spray) and low (1.5 μg/kg per spray) nicotine dose sprays, respectively. Self-administration of the placebo spray significantly exceeded that of each nicotine spray ($P<0.05$ for both comparisons versus placebo). In the free choice session, 39% of the choices were of the placebo spray, 19% were of the very low dose nicotine spray, and 42% were of the low dose nicotine spray. Statistical tests showed that the very low dose spray was self-administered significantly less than either the placebo or the low nicotine dose spray, whereas the latter two did not differ between them. As the authors themselves note, this study does not support nicotine self-administration in smokers. In fact, in the sampling sessions, nicotine appears to have been aversive to the participating smokers, despite overnight smoking abstinence designed to lead to nicotine deprivation.

Discussion

This article examined the empirical basis of the commonly repeated statement that "self administration of nicotine in isolation from tobacco smoke has been shown in smokers not trying to quit, using intravenous [...], oral [...] and nasal [...] routes of administration" (Caggiula et al. 2001, p. 516). Taking off from the studies cited to support the above statement and expanding to all relevant studies we were able to locate, the present review does not support this commonly repeated statement. The two widely cited studies of IV self-administration (Henningfield and Goldberg 1983; Henningfield et al. 1983) included a total of ten smokers, of which seven had a history of illicit drug use. The methodology and results of these studies are very problematic, and do not support their claim as demonstrating intravenous nicotine self-administration in smokers. In the study of nicotine gum by Hughes and colleagues, smokers tended to prefer the placebo to the nicotine gum. Finally, in the series of studies by Perkins and his colleagues, self-administration rates of nicotine nasal spray never exceeded those of the placebo, and in some cases, nicotine appears to have been punishing even to abstinent smokers.

Before proceeding with the discussion, it is important to note that the results of the nicotine self-administration studies reviewed above are manifestly different from those obtained in studies using a similar methodology in other drugs. For example, Foltin and Fishman (1992) used a choice procedure to compare the reinforcing properties of intravenous and smoked cocaine. When pitted against placebo, all the participants (cocaine users) chose either intravenous or smoked cocaine about 90% of the times. In a study of ethanol, using a choice procedure very much like Perkins and colleagues', ethanol was chosen over placebo 60% of the time (De Wit and McCracken 1990). This is despite the fact that in contrast to the nicotine studies, the participants in the ethanol study were light to medium drinkers who did not meet criteria for alcohol dependence and were not required to abstain for a significant period of time.

The conclusion that smokers do not self-administer pure nicotine is especially remarkable considering that there are reasons to expect that smokers would self-administer nicotine even if it were not a primary reinforcer. In the past 2 decades, smokers were consistently exposed to the message that smoking equals nicotine addiction and that nicotine is as addictive as cocaine and heroin. It would be difficult to find smokers who do not adhere to this view, and probably impossible to find participants for nicotine studies who were not at least very familiar with it. Given that smokers are often able to recognize the psychoactive and peripheral effects of nicotine (Hughes et al. 1985; Perkins et al. 1994a, 1996a, 1997b), it follows that pharmacologically inert placebos such as saline (in the case of intravenous nicotine), placebo chewing gum without nicotine, or nicotine-free nasal spray cannot control for the potential effects of smokers' beliefs and expectations regarding nicotine. Such beliefs and expectations are likely to affect behavioral and subjective responses in smoking studies. Indeed, studies have shown that manipulating smokers' expectations can dramatically alter self-administration rates as well as subjective reports of the effect of smoking and nicotine (Hughes et al. 1985; Juliano and Brandon 2002).

In light of these considerations, the fact that the studies we reviewed do not show self-administration of pure nicotine by smokers, despite the lack of an active placebo, is clearly inconsistent with the view that nicotine is a powerful primary reinforcer. Several authors of the studies we reviewed appear to recognize this difficulty and attempt to resolve it. Henningfield and coworkers, for example, justify their claim for nicotine self-administration in their studies by arguing that, whereas participants administered both nicotine and saline, "nicotine injections occurred in regular patterns whereas saline injections occurred with wide variability in pattern and frequency both within and across subjects" (Henningfield and Goldberg 1983, p. 1022). This claim, however, is of doubtful relevance and, as shown above, is not backed by evidence. Perkins et al. (1996b) subdivided their participants into those who self-administered nicotine and those who did not, proceeding to analyze the data of the latter group ("nicotine choosers"). This post-hoc analysis, however, has no bearing on the question whether smokers, as a population, self-administer nicotine. It should be

possible in any study to find a subset of participants who behave as predicted, and while it may be interesting to explore the attributes of such a subset, this cannot constitute a confirmation of the research hypothesis.

One explanation that is commonly proposed to account for the failure of pure nicotine to induce self-administration or positive mood has been that the reinforcing properties of nicotine depend on the speed with which it reaches the brain. This "nicotine delivery kinetics" hypothesis was proposed by Henningfield and Keenan (1993), and while it is very commonly cited, its validity has never been established. As space limitation precludes a thorough discussion of this hypothesis, we shall briefly mention only three counter-arguments. First, systematic comparisons of the subjective reward associated with various nicotine delivery devices (Hajek et al. 1999; West et al. 2000, 2001) demonstrated that the nasal spray, the fastest delivery NRT, was the most aversive, while the slowest one, the nicotine patch, was the least aversive. Second, Rose et al. (2000) demonstrated that "rapid boli" of IV nicotine did not differ from continuous administration, both being less rewarding and reducing craving less than denicotinized cigarettes. Finally, even if the nicotine delivery kinetics had merit, the major body of research we reviewed here involved the nicotine nasal spray, which was expressly chosen due to its fast delivery kinetics; as we have documented, it was never preferred to placebo even by abstinent smokers.

It may also be argued that nicotine was not self-administered in the studies reviewed here because of the aversive properties of the nicotine delivery devices. Specifically, the irritation of the veins associated with injections, the bad taste of the gum, the burning sensation in the nostrils caused by the spray, or the skin irritation associated with the patches may have counteracted any reinforcing properties of nicotine. However, this explanation ignores the fact that most of the reported studies have made considerable efforts to match the placebo and the nicotine devices on these properties. More importantly, this argument cannot be turned around to conclude that nicotine-self administration in fact did take place in these studies.

This review is consistent with recent studies that have challenged the primary role ascribed to nicotine in explaining the persistence of smoking and the difficulties involved in quitting. As summarized in the Introduction to this review, the results of these studies have questioned the reward value of nicotine, on the one hand and documented alternative, non-drug mechanisms that appear to drive smoking, on the other. Because of the mounting challenges to the nicotine addiction thesis, the alleged self-administration of pure nicotine by smokers has become a cornerstone of the theory that nicotine is a powerful reinforcer in humans. The failure of smokers to self-administer nicotine, as documented here, especially in a fast delivery form like nasal spray and following smoking abstinence, calls for a critical re-evaluation of the nicotine addiction thesis.

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