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Review

Does nicotine do what we think it does? A meta-analytic review of the subjective effects of nicotine in nasal spray and intravenous studies with smokers and nonsmokers

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We conducted a meta-analysis of placebo-controlled laboratory studies of the subjective effects of nicotine. A total of 15 studies (11 with nasal spray, four with intravenous administration) with smokers and six studies (all with nasal spray) with never-smokers were included. Studies of other routes of administration (e.g., smoked tobacco) were not included because of insufficient numbers of available effect sizes. Meta-analysis results indicated that nicotine increased vigor for smokers but increased fatigue for never-smokers. Nicotine increased head rush for both smokers and never-smokers. In studies of smokers only, nicotine also increased ratings of drug high and drug liking. Contrary to expectations, nicotine decreased relaxation and increased tension/jitteriness for both smokers and never-smokers. Dose–response relationships were most clearly observed for head rush and drug high. Considerable variability was found across studies for a given nicotine dose and route of administration. Implications of the current findings about the role of subjective effects in nicotine reinforcement and self-administration are discussed along with commentary on methodological issues and recommendations for future studies.

Introduction

Despite the increasing prevalence and sophistication of public health interventions, approximately 22% of the U.S. population smokes cigarettes (Schiller, Coriaty-Nelson, & Barnes, 2004). In addition, adolescents who begin smoking are likely to become nicotine dependent (Breslau, Johnson, Hiripi, & Kessler, 2001), only about 40% of smokers attempt to quit in a given year (Centers for Disease Control and Prevention, 2002), and about 70% of smokers enrolled in state-of-the-art smoking cessation programs relapse within a year (Fiore et al., 2000). Clearly, cigarette smoking is a highly persistent behavior that is relatively easy to start and relatively difficult to stop. Stated more formally, smoking is a highly reinforcing behavior.

Studies consistently find that smokers believe smoking has a mood-enhancing effect (Brandon & Baker, 1991; Gilbert, Sharpe, Ramanaiah, Detweiler, & Anderson, 2000; M. A. H. Russell, Peto, & Patel, 1974). For example, Gilbert et al. (2000) asked smokers to indicate the percentage of time they smoked in a variety of situations tapping different smoking motives. Participants reported that they smoked 73% of the time when anxious, followed by 66% of the time to enhance pleasure and 64% of the time to reduce negative affect. In field studies, smokers reported the alleviation of negative affect immediately following smoking (e.g., Parrott, 1993, 1995). These studies suggest that the reinforcing effects of smoking are mediated partly by its mood-

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enhancing effects. However, findings from these studies are only suggestive because they were unable to control for expectancy effects or determine whether reported subjective effects were related specifically to nicotine.

Research also suggests that people who briefly experiment with smoking as adolescents or young adults may be less sensitive to the positive subjective effects of smoking than their peers who progress to regular smoking. O. F. Pomerleau, Pomerleau, and Namenek (1998) asked regular smokers and people who experimented only briefly with smoking as adolescents or young adults about their reactions to the first cigarette they ever smoked. The experimenter-only group was significantly less likely to report experiencing a pleasurable buzz or rush upon smoking their first cigarette and fewer pleasurable sensations; unpleasant sensations upon smoking did not differ between groups. C. S. Pomerleau, Pomerleau, Namenek, and Marks (1999) reported a similar finding. However, findings from retrospective studies can only be suggestive because these studies are subject to recall bias in addition to having the limitations of survey studies. By contrast, laboratory studies can be designed to overcome these limitations.

The subjective effects of nicotine, the principal psychoactive ingredient in tobacco smoke, have been investigated in numerous placebo-controlled laboratory studies with smokers and nonsmokers (see review by Kalman, 2002). Studies with nonsmokers can help us understand the role of nicotine's subjective effects in smoking initiation. These studies also are well suited to examine the psychoactive effects of nicotine that cannot be attributed to withdrawal relief (e.g., effects that are the result of positive reinforcement). By contrast, studies with smokers are well suited to investigate the role of nicotine's subjective effects in smoking maintenance (i.e., after the development of chronic tolerance and possibly sensitization to some subjective effects). However, these studies are unable to clearly distinguish between effects related to positive versus negative reinforcement (Gilbert & McClernon, 2000; Kalman, 2002; Pritchard & Robinson, 2000).

In addition, the magnitude of an effect will be influenced by dose. In particular, dose may influence the direction of the effect, i.e., the dose–response curve may be curvilinear rather than linear. For example, nicotine may have mild positive effects at low doses, moderate positive effects at intermediate doses, and negative effects at high doses (Perkins, Grobe, Weiss, Fonte, & Caggiula, 1996). The direction of the effect also may differ according to whether tolerance to the aversive effects of nicotine has been acquired. Accordingly, the effects for smokers may be positive whereas those for nonsmokers may be negative. The magnitude of the subjective effects of nicotine (including whether any subjective effects are even produced) also may depend, in part, on how rapidly peak systemic levels of nicotine are reached following administration. As a result, a cigarette is expected to produce effects more quickly than a nicotine patch, and the magnitude of the effect also may be greater from a cigarette versus patch. In other words, the subjective effects of nicotine are likely to be influenced by the route of administration.

A review of placebo-controlled laboratory studies found only weak evidence for the mood effects of nicotine (Kalman, 2002; Kassel, Stroud, & Paronis, 2003). For example, few studies across routes of administration and dose reported a significant main effect of nicotine on relaxation or tension reduction. However, sample sizes in these studies were often small. For example, 16 of 26 studies with smoked tobacco and 10 of 12 nasal spray studies included fewer than 20 participants (see Tables 2 and 3 in Kalman, 2002). Six of seven studies with intravenous or subcutaneous nicotine included fewer than 20 participants. Many of these studies may have lacked the statistical power to detect any but large effects. Yet the mood effects of nicotine appear to be relatively small and subtle. A meta-analysis of findings from these laboratory studies may be needed to demonstrate these effects.

The present meta-analytic study focused on the subjective effects of nicotine via nasal spray and intravenous administration for smokers and nonsmokers. We found a sufficient number of available effect sizes for these routes of administration to conduct meta-analyses (see next section). Our objectives were to investigate the direction and size of these effects as well as the consistency of effects across studies. We hypothesized that the effects in smokers would be largely positive (e.g., to increase relaxation and decrease tension) but that they would be generally negative in nonsmokers. We also investigated the effect of nicotine dose on subjective effects.

Method

Search strategy for identifying studies

The following search strategies were used to identify candidate studies for this review: (a) MEDLINE (January 1970 to June 2003) and PsycLIT (January 1967 to June 2003) searches were conducted using the following keywords: Nicotine and subjective effects, nicotine and affect, nicotine and mood, smoking and subjective effects, smoking and affect, smoking and mood, nicotine reinforcement, smoking reinforcement. All published papers identified by the searches were obtained. (b) References within the studies

identified by the computer search were examined for additional relevant studies. (c) Experts in the field were contacted in an effort to identify papers in press.

Studies included in review

Studies identified by the search strategies were examined to determine their eligibility for inclusion. Studies that met the following selection criteria were included in the present review: (a) Studies were conducted in a laboratory setting, (b) a within-subjects design was used, (c) studies were double blind and placebo controlled, (d) standard doses were administered across participants, (e) a single dose (e.g., placebo) was administered in each session, although the dose could be administered more than once within the session, (f) the subjective effects of nicotine were assessed, (g) the period of time elapsed between nicotine dose administration and the measurement of subjective effects was specified, and (h) papers were written in English.

The vast majority of studies identified for potential inclusion in the meta-analysis were within-subjects designs in which dose effects were based on change scores (predose score minus postdose score). A small number of studies did not use change scores; instead, a placebo postdose mean (and standard deviation) was reported as were postdose means (and standard deviations) for active doses (e.g., Gillin, Lardon, Ruiz, Golshan, & Salin-Pascual, 1994; Kumari, Cotter, Checkley, & Gray, 1997). Effect sizes for these studies are not directly comparable with the effect sizes from the within-subjects designs because of the lack of predose means and standard deviations. Thus we included only studies for which change score data (mean change and standard deviation of the difference scores) were available either in the published article or from the authors.

A total of 50 unique (i.e., nonredundant) studies of smokers and 17 studies of never-smokers meeting these criteria were identified. Of the 50 studies of smokers, 41 of them involved smokers who were significantly nicotine deprived prior to testing (i.e., nicotine deprived for at least 2 hr prior to the session). In the remaining nine studies, smokers were minimally nicotine deprived prior to testing (i.e., nicotine deprived for at least 15 min but no more than 2 hr). The use of a 2-hr cutoff to distinguish between significantly nicotine-deprived and minimally nicotine-deprived smokers for the purposes of classification is based on the metabolic half-life of nicotine, which is approximately 2 hr in smoked tobacco (Benowitz, 1988). However, the half-life of nicotine varies among individuals, ranging from 1 to 4 hr (Benowitz, Jacob, Jones, & Rosenberg, 1982). Never-smokers smoked fewer than 100 cigarettes in their lifetime. Studies that included more than one type of participant were placed in all relevant categories.

Among studies with never-smokers, three studies used intravenous or subcutaneous administration, seven studies used nasal spray, three studies used gum, three studies used the patch, and one study used the inhaler. Data for all seven studies with nasal spray were available for the meta-analyses. One study using subcutaneous administration (Foulds et al., 1997) and one study using gum (Heishman, Snyder, & Henningfield, 1993) were excluded because of measurement problems (see The dependent variable section). To increase the reliability of the d_+ statistic and maximize the number of possible combined-effect sizes, we set the minimum number of effect sizes required to conduct a meta-analysis to three (see Data analysis section). Therefore, meta-analyses focused on nasal spray studies. One of these studies (Perkins, Grobe, Stiller et al., 1994) was excluded because it assessed only pain perception. Therefore, six nasal spray studies were included in the meta-analyses of studies with never-smokers.

Among studies with significantly nicotine-deprived smokers, five studies used intravenous or subcutaneous administration, 13 studies used nasal spray, four studies used gum, two studies used the patch, and 16 studies used smoked tobacco. One intravenous study (Foulds et al., 1997) was excluded because of measurement problems. One of the 13 nasal spray studies was excluded because the data needed to calculate effect sizes were not available (Perkins, Sexton, Reynolds et al., 1994). Another study (Perkins, Grobe, Stiller et al., 1994) was excluded because it assessed only pain perception. However, the data needed for calculating effect sizes were available for only one of 16 studies using smoked tobacco. Of these studies, 12 were published 10 or more years ago and the authors no longer had access to the data. Therefore, it was not possible to conduct meta-analyses of these studies. The data needed for calculating effect sizes were available for only two of the four studies using gum, and only two patch studies meeting study criteria have been reported. However, as noted above, we set the minimum number of effect sizes required to conduct a meta-analysis to three (see Data analysis section). Therefore, meta-analyses focused on 11 nasal spray and four intravenous studies.

Among studies with minimally nicotine-deprived smokers, one study used intravenous administration, no study used nasal spray, one study used gum, and seven studies used smoked tobacco. The number of studies using intravenous administration or patch was insufficient to conduct meta-analyses. In addition, the data needed for calculating effect sizes were available for only two of seven studies using smoked

tobacco. Therefore, it was not possible to conduct meta-analyses of studies with minimally nicotine-deprived smokers.

Table 1 presents the characteristics of participants in the studies included in the meta-analyses. Table 2 presents key design characteristics of the studies included in the meta-analyses. Participants in the studies with intravenous nicotine were cocaine dependent, whereas smokers with a history of a non-nicotine drug use disorder were excluded from participating in the nasal spray studies. Hughes, Rose, and Callas (2000b) reported that nicotine gum was more reinforcing for smokers with a history of alcoholism than in smokers without this history. Although only a few between-group differences were observed for the subjective effects of nicotine, these findings suggest that smokers with versus without a history of cocaine dependence may respond differently to nicotine. Research in this area is needed.

Classification of dose

For nasal spray, we defined the placebo, very low, low, and medium doses as 0, 6, 12, and 20 μg/kg, respectively. The active doses produce venous blood plasma levels of approximately 5, 10, and 15 ng/ml, respectively (Perkins, Grobe, Fonte et al., 1994). A cigarette delivering 1 mg of nicotine will produce a peak nicotine plasma level of approximately 16 ng/ml (Gourlay & Benowitz, 1997a). Three nasal spray studies did not include a 12-μg/kg dose. For two of these studies (Perkins, Gerlach, Broge, Grobe et al., 2001; Perkins, Gerlach, Broge, Grobe, & Wilson, 2000) we used 10 μg/kg as the medium dose; and for one study (Perkins, Sexton, Stiller et al., 1994) we used 15 μg/kg as the medium dose. In addition, one study (Perkins et al., 1993) did not include a 20-μg/kg dose. For this study we used a 30-μg/kg dose as the high dose. The maximum dose used in any nasal spray study was 30 μg/kg. In their studies, Perkins and colleagues used doses ranging from 3 to 30 μg/kg.

The studies with intravenous administration included a total of five doses (in addition to placebo dose). Two of these doses (0.75 mg/70 kg and 1.0 mg/70 kg) produce a plasma level of approximately 15 ng/ml and, therefore, correspond to the medium dose for nasal spray. Two other doses (1.5 mg/70 kg and 2.0 mg/70 kg) produce a plasma level of approximately 25–30 ng/ml and were labeled "high dose." The fifth dose (3.0 mg/70 kg) produces a plasma level of approximately 45 ng/ml and was labeled "very high dose." However, only two studies included a very high dose; as already noted, a minimum of three studies was required for the meta-analyses. Thus we created five dose categories: Placebo, very low, low, medium, and high. In addition to placebo dose, nasal spray studies included doses in the first three categories and intravenous studies included doses in the last two categories.

Table 1. Characteristics of participants in the studies included in the meta-analyses.

Participant type and study	Route of administration	Total *n*	Age (years)[a]	Percent female	Mean (*SD*) cigarettes/day
Smokers[b]					
Chausmer et al. (2003)[c]	Intravenous	10	38.9	0	18 (NA)
Garrett & Griffiths (2001)[c]	Intravenous	9	Range=28–39	22	>20
Jones et al. (1999)[c]	Intravenous	10	35	20	25 (NA)
Jones & Griffiths (2003)[c]	Intravenous	9	37	0	18 (NA)
Grobe et al. (1998)	Nasal spray	12	22.9	50	18.3 (9.9)
Perkins et al. (1993)	Nasal spray	8	20.4	50	22.4 (6.8)
Perkins, DiMarco et al. (1994)	Nasal spray	18	22.6	50	18.5 (4.2)
Perkins, Grobe, Fonte et al. (1994)	Nasal spray	17	21.2	47	21.2 (6.2)
Perkins, Sexton, Stiller et al. (1994)	Nasal spray	19	21.3	53	19.1 (3.1)
Perkins et al. (1995)	Nasal spray	18	22.3	50	17.7 (2.1)
Perkins et al. (1996) study 1	Nasal spray	24	22.8	67	19.7 (4.9)
Perkins, Grobe et al. (1997)	Nasal spray	10	30.6	50	23.4 (7.0)
Perkins, Sanders et al. (1997)	Nasal spray	11	23.0	46	20.1 (NA)
Perkins et al. (2000)	Nasal spray	55	32.7	83	21.4 (6.4)
Perkins et al. (2001)	Nasal spray	45	38.3	67	21.3 (6.7)
Never-smokers					
Grobe et al. (1998)	Nasal spray	11	25.1	55	—
Perkins et al. (1993)	Nasal spray	7	23.7	57	—
Perkins, Grobe, Fonte et al. (1994)	Nasal spray	18	23.25	50	—
Perkins, Sanders et al. (1997)	Nasal spray	10	21.9	50	—
Perkins et al. (2000)	Nasal spray	37	28.8	49	—
Perkins et al. (2001)	Nasal spray	19	34.0	47	—

Note. NA, not available.
[a]Values are means, unless otherwise noted.
[b]Participants in these studies were nicotine deprived for at least 2 hr at the time of testing; in most studies, testing occurred following overnight nicotine deprivation.
[c]Smokers in these studies were also cocaine dependent.

Table 2. Design characteristics of the studies included in the meta-analyses.

Participant type and study	Measure (subjective effect)	Nicotine doses included in meta-analyses, μg/kg[a]
Smokers[b]: Intravenous		
Chausmer et al. (2003)	VAS (head rush, high, like)	0, 28
Garrett & Griffiths (2001)	VAS (relaxed, drowsy, head rush, high, like)	0, 11, 22
Jones & Griffiths (2003)	VAS (relaxed, drowsy, head rush, high, like)	0, 14, 28
Jones et al. (1999)	VAS (relaxed, drowsy, head rush, high, like)	0, 11, 22
Smokers[b]: Nasal spray		
Grobe et al. (1998)	POMS (vigor, fatigue, tension, head rush)	0, 20
Perkins et al. (1993)	VAS (relaxed)	
	POMS (Vigor, fatigue, tension)	0
Perkins, DiMarco et al. (1994)	VAS (head rush)	
	POMS (jittery)	0, 12
Perkins, Grobe, Fonte et al. (1994)	VAS (relaxed, head rush)	
	POMS (vigor, fatigue, tension)	0, 20
Perkins, Sexton, Stiller et al. (1994)	VAS (relaxed)	
	POMS (vigor, fatigue, tension)	0, 15
Perkins et al. (1995)	VAS (relaxed, head rush)	
	POMS (vigor, fatigue, tension)	0, 20
Perkins et al. (1996) study 1	VAS (relaxed)	
	POMS (vigor)	0, 9
Perkins, Grobe et al. (1997)	VAS (relaxed)	
	POMS (vigor)	0
Perkins, Sanders et al. (1997)	VAS (relaxed, jittery, head rush)	
	POMS (vigor, fatigue)	0, 12, 20
Perkins et al. (2000)	VAS (relaxed, jittery, head rush)	
	POMS (vigor, fatigue)	0, 10, 20
Perkins et al. (2001)	VAS (relaxed, head rush)	
	POMS (vigor, tension)	0, 10, 20
Never smokers: Nasal spray		
Grobe et al. (1998)	VAS (head rush)	
	POMS (vigor, fatigue, tension)	0, 20
Perkins et al. (1993)	VAS (relaxed, head rush)	
	POMS (vigor, fatigue, tension)	0, 30
Perkins, Grobe, Fonte et al. (1994)	VAS (relaxed, head rush)	
	POMS (vigor, fatigue, tension)	0, 20
Perkins, Sanders et al. (1997)	VAS (relaxed, head rush)	
	POMS (vigor, fatigue, tension)	0, 10, 20
Perkins et al. (2000)	VAS (relaxed, head rush)	
	POMS (vigor, fatigue, tension)	0, 10, 20
Perkins et al. (2001)	VAS (relaxed, head rush)	
	POMS (vigor, fatigue, tension)	0, 10, 20

Note. VAS, Visual Analogue Scale; POMS, Profile of Mood States (McNair, Lorr, & Droppleman, 1971).
[a]Intravenous doses were reported in papers as mg/70 kg. To ease comparison with nasal spray studies, we converted these doses to μg/kg.
[b]Smokers in these studies were nicotine deprived for at least 2 hr at the time of testing; in most studies, testing occurred following overnight nicotine deprivation.

The dependent variable

The circumplex model of affect (e.g., Feldman Barrett, & Russell, 1998) guided the process of coding mood terms in the present study. According to this model, the basic structure of mood, or "core affect," can be captured by two dimensions: Affective valence (pleasant and unpleasant) and arousal (high arousal and low arousal). Affective space can be divided into octants (e.g., pleasant–high arousal, pleasant–low arousal, unpleasant–high arousal, unpleasant–low arousal; Yik, Russell, & Feldman Barrett, 1999, p. 602). (Note that Feldman Barrett and colleagues also use the term *activation* in describing the arousal dimension of affect, thus high and low arousal are described as high and low activation, respectively.) In the present study, mood terms were coded according to the octant into which they fell. For example, relaxed and calm were both coded "pleasant–low arousal," whereas tension and jittery were both coded "unpleasant–high arousal." Similarly, vigor was coded "pleasant–high arousal" and fatigued was coded "unpleasant–low arousal." Finally, affect terms may be neutral with respect to arousal (e.g., pleasant, unpleasant) or valence (e.g., stimulated, drowsy). This approach has the important advantage of bringing conceptual order to the large number of affects measured across studies. In addition to mood, nasal spray and intravenous studies assessed head rush, and the intravenous studies also assessed drug high and drug liking.

Two studies (Foulds et al., 1997; Heishman et al., 1993) were excluded from the analyses because of measurement problems. Foulds et al. (1997) used the Bond–Lader mood scales to measure subjective effects. Some items in these scales were not clearly

related to the construct being measured, however. For example, the alertness scale contains the items "well-coordinated/clumsy" and "incompetent/proficient." In addition, all items on these scales, as well as the scales themselves, are bipolar, whereas items and scales for all other measures we included are unipolar. Heishman et al. (1993) used the Addiction Research Center Inventory to measure subjective effects. Again, some items (e.g., I feel very patient, I feel more clear headed than dreamy) in these scales were not clearly related to the construct being measured and could not be coded into any octant.

The present study focused on mood states in four of the eight octants of the circumplex model. These states are vigor in pleasant–high arousal; relaxed in pleasant–low arousal; fatigued, drowsiness, or tired in unpleasant–low arousal; and tension or jittery in unpleasant–high arousal. A sufficient number of effect sizes were available to conduct meta-analyses of the effect of nicotine dose on these mood states. In addition, meta-analyses were conducted for the subjective effects of head rush, drug high, and drug liking.

Statistical methods

For each study included in the meta-analysis, we tabulated the mean difference between the predose mood score and the postdose mood score (repeated measures) for each available dose level (placebo, low, medium, and high), mood octant, and route of administration included in the study. In addition, we tabulated the standard deviation of the difference scores for each mean difference. We computed individual effect sizes uncorrected for sample size bias as the mean difference divided by the standard deviation of the difference scores. These uncorrected effect sizes (commonly known as g) were then corrected for sample size using the DSTAT software program (Johnson, 1989). DSTAT also was used to statistically combine the corrected effect sizes (or d values) into composite effect sizes (d_+) and to evaluate homogeneity of effect sizes. The formulas used in DSTAT to compute individual d values, d_+ values, corresponding 95% confidence intervals, and the Q statistic are derived from Hedges and Olkin (1985).

Homogeneity of effect sizes was evaluated by means of the Q statistic that follows a chi-square distribution with k–1 degrees of freedom, where k is the number of independent effect sizes being statistically combined. DSTAT identifies outlier effect sizes on the basis of greatest reduction in the Q statistic value. The magnitude of the Q statistic reduction for a given outlier effect size depends on discrepancy from other effect sizes and on sample size. Thus discrepant effect sizes based on larger sample sizes may result in greater Q statistic reduction relative to a similarly discrepant effect size based on a smaller sample size. Composite effect sizes found to be statistically heterogeneous by the Q statistic were iteratively recomputed by omitting outlier effect size(s) from the analysis until a statistically nonsignificant Q statistic was obtained. In no analysis was it necessary to remove more than two outlier effect sizes to achieve homogeneity.

For purposes of the meta-analysis, a minimum of three effect sizes was required to compute a composite effect size. Examination of the number of available effect sizes for all planned meta-analyses revealed that sufficient numbers of effect sizes were available only for three sets of analyses: Nasal spray tested in smokers, intravenous nicotine tested in smokers, and nasal spray tested in never-smokers. Within each set of analyses, not all possible composite effect sizes were computed because of the lack of a sufficient number of effect sizes for all eight octants.

The statistical significance of combined-effect sizes was tested by means of an SPSS macro program written by David B. Wilson (macro program MEANES.SPS; Lipsey & Wilson, 2001) that computes a z-test statistic. Bias-corrected effect sizes from DSTAT and effect size variances (computed according to formulas provided in the DSTAT manual) were entered into the SPSS macro program. In addition, we tested the statistical significance of the difference between smoker and never-smoker combined-effect sizes for nasal spray separately for each mood octant. These between-group analyses are appropriate because all of the effect sizes in a given analysis were independent. In contrast, dose comparisons were not possible because necessary information (e.g., the correlation between scores for each pair of dose levels to be compared) was not available. In addition, there are typically differing numbers of effect sizes for each set of dependent (correlated) combined-effect sizes (i.e., only a small number of studies contributed effect sizes at all three dose levels for a given mood octant measure; some studies contributed to only one or two dose-level combined-effect sizes) and, as such, this presents computational difficulties for testing dose effects directly. No between-group analyses for nasal spray versus intravenous nicotine were computed because active doses overlapped only partially and because the number of intravenous nicotine effect sizes was small. Between-group analyses (smoker vs. nonsmoker for nasal spray studies) were computed by means of another SPSS macro program written by David B. Wilson (macro program METAF.SPS; Lipsey & Wilson, 2001) that computes a Q statistic analog of fixed-effects between-group analyses of variance (ANOVAs).

A total of 45 combined-effect sizes were computed consisting of 15 effect sizes for smoker nasal spray studies, 15 effect sizes for never-smoker nasal spray studies, and 15 effect sizes for smoker intravenous nicotine studies. To control for inflation of Type I error rate, we set α equal to .001 (essentially a Bonferroni correction within each set of 15 combined-effect sizes) for purposes of interpreting the statistical significance of the combined-effect size z-tests. For the between-group analyses, we considered each mood octant to constitute a set or family of three conceptually related comparisons: Smoker versus never-smoker at each of three dose levels. Thus we set α equal to .0167 (representing a Bonferroni correction within each set of three between-group analyses) for purposes of interpreting the statistical significance of the ANOVAs.

Results

Subjective effects of nicotine via nasal spray

Smokers. Table 3 reports test statistics, including composite effect sizes (d_+), confidence intervals for d, and the z-test for statistical significance of combined-effect sizes, by mood octant and dose level for nicotine nasal spray in smokers. Findings for head rush also are presented. For these smoker meta-analyses, study sample sizes ranged from 8 to 55 (total number of subjects=237; mean sample size across the 11 studies=21.5). Too few effect sizes were available in these studies for very-low-dose or high-dose meta-analyses. As a result, composite effect sizes are available only for the placebo, low-dose, and medium-dose conditions.

For pleasant–low arousal in the smoker nasal spray studies, the placebo-dose combined-effect size (+.13) was not significantly different from baseline, whereas the low-dose effect size (−.39) and the medium-dose effect size (−.51) were significantly different from baseline. These findings indicate that nicotine via nasal spray produces a decrease in feelings of relaxation. The pattern of composite effect sizes suggests a dose-related increase in effect, but we were not able to test such a dose–response relationship directly because of limitations in the data (see Statistical methods section). For pleasant–high arousal, both active dose combined-effect sizes were statistically significant, whereas the placebo dose was statistically nonsignificant. These findings indicate that nicotine via nasal spray produces an increase in feelings of vigor in smokers, although a dose-related increase in effect does not appear to exist across the three doses.

For unpleasant–low arousal, the nasal spray data show that smokers experienced a significant decrease in fatigue under the placebo dose versus baseline condition. Active doses produced nonsignificant decreases in fatigue relative to baseline. For unpleasant–high arousal, the combined-effect size for the placebo dose was nonsignificant, whereas the effect sizes for low and medium doses for both groups were significantly different relative to baseline. That is, active doses appear to have modestly increased tension relative to placebo.

For head rush, all three dose levels produced an effect that was significantly different from baseline. Also, a dose–response relationship appears to exist for smokers such that active doses of nicotine produced reports of greater levels of head rush. A large effect size (+.92) was observed for medium-dose nicotine.

Never-smokers. Table 4 reports test statistics, including composite effect sizes (d_+), confidence intervals for d, and the z-test for statistical significance of combined-effect sizes, by mood octant and dose level for intravenous nicotine in smokers. Study sample sizes ranged from 7 to 37 (total number of subjects=102; mean sample size across the six studies=17.0). As with the smoker nasal spray studies, too few effect sizes were available in these studies for very-low-dose or high-dose meta-analyses. As a result, composite effect sizes are available only for the placebo, low-dose, and medium-dose conditions.

For pleasant–low arousal, all three doses significantly decreased feelings of relaxation, although the difference was at the level of a trend for the placebo dose. For pleasant–high arousal, the medium dose of nicotine significantly decreased feelings of vigor. The combined-effect size for the low dose almost reached statistical significance. Although the combined-effect sizes for the low and medium doses were similar, the analysis for medium dose, which was based on six effect sizes, had greater statistical power than the analysis for low dose, which was based on three effect sizes. For unpleasant–low arousal, although increases in fatigue were observed, none of the doses were significantly different from baseline. For unpleasant–high arousal, the composite effect sizes for the two active doses were large and significantly different from baseline. For head rush, all three doses were significantly different from baseline. In addition, the pattern of composite effect sizes suggested that a dose–response relationship existed across the three doses; interestingly, however, all three composite effect sizes were large.

Smokers versus never-smokers. As discussed above, we used analyses based on the Q statistic (analogous to fixed-effects ANOVAs) to investigate the existence of significant differences in the subjective effects of nicotine for smokers versus never smokers. For pleasant–low arousal, the between-group comparisons for smoker versus nonsmoker at each of the

Table 3. Composite effect sizes (d_+), 95% confidence intervals (*CI*) for d_+, *z*-test for statistical significance, homogeneity statistics, and individual effect sizes (*d*) by mood octant and dose level for nicotine nasal spray in smokers.

Mood octant	Placebo	Low dose	Medium dose
Pleasant–low arousal (relaxed)	d_+=+.13 (*CI*: −.07/+.34) *z*=1.30, *p*=.19 (Q(7)=2.55, *p*=.92) (*n*=8 effect sizes: −.09, −.04, +.03, +.07, +.16, +.22, +.27, +.63)	d_+=−.39 (*CI*: −.61/−.16) *z*=−3.32, *p*=.0009 (Q(4)=6.82, *p*=.15) (*n*=5 effect sizes: −.82, −.53, −.44, −.35, +.23)	d_+=−.51 (*CI*: −.75/−.28) *z*=−4.30, *p*<.0001 (Q(4)=1.87, *p*=.76) (*n*=5 effect sizes: −.67, −.63, −.58, −.45, −.29)
Pleasant–high arousal (vigor)	d_+=+.26 (*CI*: +.07/+.44) *z*=2.65, *p*=.0080 (Q(9)=5.4, *p*=.79) (*n*=10 effect sizes: −.26, +.00, +.11, +.12, +.13, +.16, +.25, +.29, +.53, +.74)	d_+=+.40 (*CI*: +.18/+.63) *z*=3.52, *p*=.0004 (Q(4)=2.30, *p*=.68) (*n*=5 effect sizes: +.14, +.18, +.32, +.49, +.60)	d_+=+.37 (*CI*: +.15/+.60) *z*=3.28, *p*=.0010 (Q(5)=2.07, *p*=.84) (*n*=6 effect sizes: +.14, +.18, +.34, +.47, +.53, +.54)
Unpleasant–low arousal (fatigue)	d_+=−.67[a] (*CI*: −1.05/−.28) *z*=−3.43, *p*=.0006 (Q(3)=1.35, *p*=.72) (*n*=4 effect sizes: −.92 −.86, −.59, −.43)	d_+=−.14 (*CI*: −.45/+.16) *z*=−.93, *p*=.35 (Q(2)=1.45, *p*=.49) (*n*=3 effect sizes: −.51, −.14, −.03)	d_+=−.25 (*CI*: −.51/−.01) *z*=−1.86, *p*=.06 (Q(4)=2.51, *p*=.64) (*n*=5 effect sizes: −.61, −.48, −.44, −.09, −.02)
Unpleasant–high arousal (tension, jittery)	d_+=+.28[b] (*CI*: +.05/+.52) *z*=2.34, *p*=.02 (Q(6)=4.21, *p*=.65) (*n*=7 effect sizes: −.16, +.09, +.17, +.33, +.34, +.70, +.83)	d_+=+.51 (*CI*: +.28/+.74) *z*=4.33, *p*<.00001 (Q(4)=1.63, *p*=.80) (*n*=5 effect sizes: +.34, +.47, +.53, +.72, +.80)	d_+=+.50 (*CI*: +.27/+.72) *z*=4.33, *p*<.00001 (Q(5)=6.43, *p*=.27) (*n*=6 effect sizes: −.03, +.21, +.45, +.62, +.73, +.81)
Head rush	d_+=+.34 (*CI*: +.12/+.55) *z*=3.06, *p*=.0022 (Q(6)=3.51, *p*=.74) (*n*=7 effect sizes: +.03, +.25, +.30, +.45, +.48, +.48, +.53)	d_+=+.63[c] (*CI*: +.30/+.96) *z*=3.75, *p*=.0002 (Q(2)=0.17, *p*=.92) (*n*=3 effect sizes: +.51, +.64, +.68)	d_+=+.92 (*CI*: +.69/+1.16) *z*=7.78, *p*<.00001 (Q(5)=5.00, *p*=.42) (*n*=6 effect sizes: +.54, +.70, +.72, +.92, +1.19, +1.22)

Note. [a]Two outliers were removed: *d*=+.08 (*n*=55) and *d*=+.55 (*n*=12) due to significant heterogeneity, Q(5)=12.27, *p*=.03.
[b]One outlier was removed: *d*=−.50 (*n*=45) due to significant heterogeneity, Q(7)=14.36, *p*=.045.
[c]One outlier was removed: *d*=+1.61 (*n*=55) due to significant heterogeneity, Q(3)=12.59, *p*=.006.

Table 4. Composite effect sizes (d_+), 95% confidence intervals for d_+, *z*-test for statistical significance, homogeneity statistics, and individual effect sizes (*d*) by mood octant and dose level for nicotine nasal spray in nonsmokers.

Mood octant	Placebo	Low dose	Medium dose
Pleasant–low arousal (relaxed)	$d_+=-.49$ (*CI*: −.81/−.16) $z=-2.89$, $p=.0039$ (Q(3)=0.16, $p=.98$) (*n*=4 effect sizes: −.64, −.51, −.48, −.36)	$d_+=-.99$ (*CI*: −1.36/−.63) $z=-5.38$, $p<.00001$ (Q(2)=1.08, $p=.58$) (*n*=3 effect sizes: −1.29, −.93, −.73)	$d_+=-1.00$ (*CI*: −1.32/−.68) $z=-6.09$, $z<.00001$ (Q(3)=1.88, $p=.60$) (*n*=4 effect sizes: −1.30, −1.12, −.93, −.55)
Pleasant–high arousal (vigor)	$d_+=-.02$[a] (*CI*: −.33/+.30) $z=-.10$, $p=.92$ (Q(3)=2.3, $p=.51$) (*n*=4 effect sizes: −.32, −.32, +.01, +.22)	$d_+=-.55$[b] (*CI*: −1.07/−.02) $z=-2.05$, $p=.0404$ (Q(1)=.14, $p=.71$) (*n*=3 effect sizes: −.69, −.48)	$d_+=-.48$ (*CI*: −.77/−.19) $z=-3.21$, $p=.0013$ (Q(4)=7.63, $p=.11$) (*n*=5 effect sizes: −1.06, −1.04, −.58, −.43, −.05)
Unpleasant–low arousal (fatigue)	$d_+=+.22$ (*CI*: −.08/−.53) $z=1.43$, $p=.15$ (Q(4)=2.13, $p=.71$) (*n*=5 effect sizes: −.19, +.15, +.18, +.19, +.28)	$d_+=+.20$ (*CI*: −.14/+.54) $z=1.15$, $p=.25$ (Q(2)=0.59, $p=.74$) (*n*=3 effect sizes: +.01, +.15, +.31)	$d_+=+.34$ (*CI*: +.06/+.63) $z=2.35$, $p=.0189$ (Q(4)=1.70, $p=.79$) (*n*=5 effect sizes: +.01, +.27, +.33, +.50, +.51)
Unpleasant–high arousal (tension, jittery)	$d_+=+.42$ (*CI*: +.11/+.73) $z=2.70$, $p=.0070$ (Q(4)=3.84, $p=.43$) (*n*=5 effect sizes: −.18, +.25, +.32, +.67, +.80)	$d_+=+1.06$ (*CI*: +.69/+1.42) $z=5.58$, $p<.00001$ (Q(2)=0.67, $p=.72$) (*n*=3 effect sizes: +.71, +1.10, +1.14)	$d_+=+.97$ (*CI*: +.67/+1.27) $z=6.31$, $p<.00001$ (Q(4)=1.64, $p=.80$) (*n*=5 effect sizes: +.67, +.82, +1.04, +1.19, +1.20)
Head rush	$d_+=+.86$ (*CI*: +.54/+1.18) $z=5.27$, $p<.00001$ (Q(4)=8.54, $p=.07$) (*n*=5 effect sizes: +.40, +.42, +.50, +.67, +1.45)	$d_+=+1.13$ (*CI*: +.76/+1.50) $z=6.04$, $p>.00001$ (Q(2)=0.30, $p=.86$) (*n*=3 effect sizes: +1.07, +1.07, +1.30)	$d_+=+1.58$ (*CI*: +1.25/+1.90) $z=9.46$, $p<.00001$ (Q(4)=3.20, $p=.52$) (*n*=5 effect sizes: +.96, +1.54, +1.57, +1.60, 2.03)

Note. [a]One outlier was removed: $d=-1.90$ ($n=7$) due to significant heterogeneity, Q(4)=8.6, $p=.07$.
[b]One outlier was removed: $d=+0.25$ ($n=37$) due to significant heterogeneity, Q(2)=5.1, $p=.077$.

three nasal spray dose levels were statistically significant: $Q(1)=9.88$, $p=.0017$ for placebo; $Q(1)=7.85$, $p=.0051$ for low dose; and $Q(1)=5.78$, $p=.0162$ for medium dose. The pattern of the magnitudes of the combined-effect sizes suggested that nonsmokers experienced significantly greater decreases in relaxation (compared with smokers) at all three doses. For pleasant–high arousal, the between-group comparisons for smoker versus nonsmoker at each of the three nasal spray dose levels were statistically significant only for the low and medium doses, $Q(1)=10.73$, $p=.0011$, and $Q(1)=20.63$, $p<.0001$, respectively. Nicotine nasal spray appears to affect smokers and nonsmokers differently such that smokers feel somewhat invigorated and nonsmokers feel the opposite.

For unpleasant–low arousal, the between-group analyses showed group differences for the placebo dose, $Q(1)=12.80$, $p=.0003$, and the medium dose, $Q(1)=8.93$, $p=.0028$; for the low dose, $Q(1)=2.19$, $p=.1390$. The pattern of results overall suggested that nicotine had a modest positive effect in ameliorating fatigue for smokers, although this interpretation assumes that the absence of nicotine would produce significant fatigue in smokers. For never-smokers, the interpretation of the results is tempered by the small number of effect sizes available for meta-analysis especially at the low dose (three effect sizes). However, it appears that nonsmokers may experience a small, though statistically nonsignificant decrease in fatigue as suggested by the positive combined-effect sizes (e.g., +.20 for low dose and +.34 for medium dose). For unpleasant–high arousal, none of the between-group analyses showed any statistically significant group differences, although the small number of effect sizes for nonsmokers may have resulted in an underpowered analysis.

For head rush, between-group analyses for nasal spray showed that nonsmokers differed from smokers for the placebo dose, $Q(1)=7.04$, $p=.0080$, and the medium dose, $Q(1)=10.18$, $p=.0014$, but not for the low dose, $Q(1)=3.94$, $p=.05$. At each dose level, never-smokers experienced greater head rush than did smokers.

Subjective effects of intravenous nicotine

As noted in the Method section, the subjective effects of intravenous nicotine have been investigated only with smokers; in addition, smokers in these studies all had histories of abuse of a non-nicotine drug. Table 5 reports test statistics, including composite effect sizes (d_+), confidence intervals for d, and the z-test for statistical significance of combined-effect sizes, by mood octant and dose level for intravenous nicotine in smokers. As in the nasal spray studies, the intravenous studies included measures of pleasant–low arousal, unpleasant–low arousal, and head rush. Findings for head rush, drug high, and drug liking also are presented. Measures of pleasant–high arousal and unpleasant–high arousal were not available in these intravenous studies. For the smoker intravenous nicotine meta-analyses, four studies were available from which effect sizes could be derived. All study sample sizes were small ($n=9$–10; total number of subjects=38).

Intravenous nicotine had no significant effect on pleasant–low arousal. None of the three dose levels was significantly different from baseline. Similar findings were obtained for the effects of intravenous nicotine on unpleasant–low arousal. However, the combined-effect size of high-dose nicotine for head rush was significantly different from baseline and corresponded to a large effect size. Similar findings were obtained for the effects of intravenous nicotine on drug high and drug liking, although the difference was at the level of a trend for the latter subjective effect. In each case, the combined-effect size of high-dose nicotine corresponded to a large effect size. In addition, a dose–response relationship appears to exist across doses for head rush and drug high.

Discussion

The present review has considered the influence of smoking status, method of nicotine administration, and dose on the effects of nicotine on subjective experience of smokers and never-smokers. Only smokers with current histories of cocaine abuse were recruited for the intravenous studies, whereas all other studies excluded smokers with substance abuse histories. In addition, the meta-analyses for nasal spray included studies with low and medium nicotine doses, whereas those for intravenous administration included studies with medium and high doses. Accordingly, the findings for these two routes of administration cannot be compared easily.

Vigor and fatigue

The meta-analysis of nasal spray studies for smokers revealed a significant increase in vigor for active nicotine doses versus baseline; the change from baseline for the placebo dose approached significance. All doses decreased fatigue, although, somewhat surprisingly, only the composite effect size of the placebo dose was significantly different from baseline. By contrast, never-smokers showed a significant decrease in vigor at the medium nicotine dose; a similar decrease in vigor was observed for the low dose but did not reach statistical significance, probably because of a lack of statistical power. No significant changes from baseline in fatigue were

Table 5. Composite effect sizes (d_+), 95% confidence intervals for d_+, *z*-test for statistical significance, homogeneity statistics, and individual effect sizes (*d*) by mood octant and dose level for IV nicotine in smokers.

Mood octant	Placebo	Medium dose	High dose
Pleasant–low arousal (relaxed)	d_+=−.28 (*CI*: −.81/+.25) *z*=−1.04, *p*=.30 (Q(2)=0.18, *p*=.92) (*n*=3 effect sizes: −.44, −.20, −.20)	d_+=−.05 (*CI*: −.57/+.48) *z*=−.17, *p*=.87 (Q(2)=0.39, *p*=.82) (*n*=3 effect sizes: −.18, −.12, +.20)	d_+=−.18 (*CI*: −.71/+.35) *z*=−.67, *p*=.50 (Q(2)=0.15, *p*=.93) (*n*=3 effect sizes: −.32, −.14, −.08)
Unpleasant–low arousal (drowsy/sleepy)	d_+=−.05 (*CI*: −.58/+.47) *z*=−.198, *p*=.84 (Q(2)=1.31, *p*=.52) (*n*=3 effect sizes: −.43, +.00, +.31)	d_+=+.08 (*CI*: −.44/+.61) *z*=.31, *p*=.75 (Q(2)=0.94, *p*=.62) (*n*=3 effect sizes: −.29, +.23, +.29)	d_+=+.28 (*CI*: −.25/+.80) *z*=1.03, *p*=.30 (Q(2)=.11, *p*=.95) (*n*=3 effect sizes: +.16, +.29, +.37)
Head rush	d_+=+.28 (*CI*: −.18/+.73) *z*=1.20, *p*=.23 (Q(3)=1.95, *p*=.58) (*n*=4 effect sizes: +.00, +.00, +.34, +.79)	d_+=+.37 (*CI*: −.15/+.90) *z*=1.39, *p*=.17 (Q(2)=0.44, *p*=.98) (*n*=3 effect sizes: +.29, +.40, +.43)	d_+=+.97[a] (*CI*: +.41/+1.52) *z*=5.02, *p*<.00001 (Q(2)=0.001, *p*=.99) (*n*=3 effect sizes: +.95, +.97, +.98)
High	d_+=+.29 (*CI*: −.16/+.75) *z*=1.27, *p*=.21 (Q(3)=2.13, *p*=.55) (*n*=4 effect sizes: .00, .00, +.37, +.82)	d_+=+.53 (*CI*: −.01/+1.06) *z*=1.94, *p*=.0521 (Q(2)=0.10, *p*=.95) (*n*=3 effect sizes: +.42, +.54, +.63)	d_+=+1.19 (*CI*: +.69/+1.69) *z*=4.72, *p*<.00001 (Q(3)=5.55, *p*=.14) (*n*=4 effect sizes: +.75, +.86, +1.16, +2.39)
Like	d_+=+.22 (*CI*: −.23/+.68) *z*=.97, *p*=.33 (Q(3)=1.03, *p*=.80) (*n*=4 effect sizes: +.00, +.00, +.36, +.53)	d_+=+.26 (*CI*: −.27/+.79) *z*=.97, *p*=.33 (Q(2)=0.56, *p*=.76) (*n*=3 effect sizes: +.00, +.28, +.50)	d_+=+.72 (*CI*: +.25/+1.19) *z*=3.04, *p*=.0024 (Q(3)=2.24, *p*=.53) (*n*=4 effect sizes: +.29, +.51, +.94, +1.24)

Note. [a]One outlier was removed: *d*=+3.38 (*n*=10) due to significant heterogeneity, Q(3)=10.31, *p*=.02.

observed for never-smokers at any dose, however. Interestingly, significant smoker versus never-smoker differences were observed for the placebo dose as well as for most active dose comparisons, suggesting that these between-group differences were related partly to the effects of route of administration as well as to nicotine itself. Finally, intravenous administration of placebo or active nicotine doses did not produce significant effects on feelings of drowsiness among smokers.

Studies have demonstrated that the effect of nicotine on arousal is state dependent (e.g., Perkins, Sexton, Stiller et al., 1994; see review, Perkins, 1999). That is, nicotine increases (pleasant) arousal when predrug arousal is low and decreases arousal when predrug arousal is high. The effects of nicotine on arousal also may be dose dependent, i.e., arousal-enhancing at moderate to high doses and arousal-reducing at very high doses (Perkins & Stitzer, 1998). Our findings are consistent with this multifactorial model. In seven nasal spray studies, smokers received a relatively low nicotine dose while at rest. Never-smokers also were at rest but received what for them would likely be experienced as a high dose because of their inexperience with and lack of acquired tolerance to nicotine. Other factors may have contributed to these findings, including smoker–never smoker differences in their innate sensitivity to nicotine (e.g., smokers may be more sensitive to the pleasant arousing effects of nicotine; Pomerleau, 1995).

Relaxation and tension/jitteriness

The meta-analysis of nasal spray studies provided little evidence that nicotine increases relaxation or decreases tension/jitteriness among smokers. Indeed, results for smokers revealed a statistically significant decrease in relaxation and a concomitant increase in tension/jitteriness compared with baseline following active dose administration. A similar pattern was observed for never-smokers. Although these effects of nicotine were even more pronounced for never-smokers, only the between-group differences for relaxation were statistically significant. No dose effect on relaxation was observed for intravenous administration with smokers. Lack of studies precluded an analysis of the effects of intravenous administration on tension/jitteriness in smokers and intravenous studies did not include never-smokers.

Findings for never-smokers probably reflect their lack of tolerance to the aversive effects of nicotine and perhaps their lack of sensitivity to the positive effects of nicotine. The findings for smokers, however, are inconsistent with the results from survey (e.g., Gilbert et al., 2000) and field studies (e.g., Parrott, 1993) and suggest that either (a) these studies did not adequately model the tension-reducing effects of nicotine or (b) nicotine does not have tension-reducing properties. One potentially important model parameter is route of administration, and nasal spray and intravenous administration may not be adequate analogues for modeling the putative tension-reducing/relaxing effects of nicotine via smoked tobacco (Gourlay & Benowitz, 1997b; see Kalman, 2002, for a discussion of issues related to methods of nicotine administration in the study of the subjective effects of nicotine). To our knowledge, only Perkins, Sexton, Reynolds et al. (1994) have directly compared the subjective effects of nicotine via smoked tobacco and nasal spray. Results were mixed and inconclusive because of limitations in the study design (e.g., control for expectancy effects was not comparable for the placebo dose between methods of administration, a measure of tension was not included in the study). Additional research is needed to more firmly determine the comparability of effects when nicotine is administered via smoked tobacco versus other methods of administration.

Head rush, drug high, and drug liking

In general, the largest effect sizes for active dose nicotine were observed for head rush. As with relaxation and tension/jitteriness, effects were more pronounced for never-smokers. Although results of the between-group comparisons were not statistically significant for low-dose nicotine, the composite effect sizes for smokers and never-smokers were +0.63 and +1.13, respectively, suggesting that the between-group analysis did not have adequate statistical power. In addition, the strongest suggestion of a linear dose–response effect for both nasal spray and intravenous administration was observed for head rush, although as noted above, significance testing of a trend could not be conducted. However, the affective valence of head rush may differ for smokers and never-smokers. In a recent study, head rush following an initial nicotine dose predicted subsequent nicotine spray self-administration for smokers but was inversely related to spray choice for never-smokers (Perkins, Gerlach, Broge, Fonte, & Wilson, 2001). This finding suggests that head rush has a positive affective valence for smokers but a negative valence for never-smokers. A linear dose–response relationship also was observed for the intravenous studies, although only the composite effect size for the high dose was statistically significant. In addition, the dose–response curve was shifted somewhat to the right relative to findings for nasal spray.

A dose–response relationship for drug high was found in the intravenous studies, although only the composite effect size for the high dose was statistically significant. In addition, the composite effect sizes (and range of individual effect sizes) for drug

high and head rush were generally similar across doses. In the studies with intravenous administration, a dose effect on drug liking was observed only for high-dose nicotine. Findings for high-dose nicotine suggest that, at least among smokers who are cocaine dependent, drug high and head rush may mediate drug liking. By comparison, no relationship was found between pleasant–low arousal or unpleasant–low arousal and drug liking in these studies.

Heterogeneity of effect sizes

As noted earlier, statistically significant heterogeneity of effect sizes was found in six of the 45 meta-analyses conducted in the present study. However, considerable variability existed in effect sizes even in the absence of statistically significant heterogeneity. For example, effect sizes for pleasant–low arousal for the placebo dose of the nasal spray for smokers ranged from −0.09 to +0.63; for the low dose they ranged from −0.82 to +0.23. Effect sizes for unpleasant–low arousal for the placebo dose of intravenous administration ranged from −0.43 to +0.31; for the low dose they ranged from −0.29 to +0.29. Differences in key study characteristics might explain this variability, including differences in study procedures, measures, or subject characteristics. However, a close examination of intravenous studies revealed few differences in subject characteristics or measures, and, although procedures differed somewhat in accordance with the objectives of the study, it seems unlikely that these differences could account for more than minor variability in effect sizes across studies.

Subject characteristics and measures also were similar across nasal spray studies. However, differences in the placebo solution could account for variability across studies in response to placebo dose. In some studies, the placebo dose consisted of a saline solution, whereas in others capsaicin, a pepper extract, was used to equate for sensory effects of the placebo and nicotine doses on nasal membranes. We hypothesized that omitting the effect sizes from studies that used capsaicin would decrease the magnitude of the combined-effect sizes for the placebo condition. To investigate this possibility, we reanalyzed the data for the placebo dose and excluded studies using capsaicin. However, the differences were generally small. For example, d_+ statistic was +0.11 for all studies and +0.14 for saline studies only. Other procedural differences (i.e., whether a single dose or two or more doses was given in a session, whether participants did or did not want to quit smoking) did not seem to account for variability in subjective responses across studies. For example, in some studies, participants attended between two and four sessions (depending on the number of doses tested in a given study) and a different dose was administered in each session. This procedure was used to minimize the possibility that the development of acute tolerance to a given dose could influence (i.e., attenuate) a participant's subjective responses to another dose. In a few studies, however, two or more doses were administered in a single session (Perkins et al., 1993; Perkins, DiMarco, Grobe, Scierka, & Stiller, 1994; Perkins, Grobe, Fonte et al., 1994; Perkins, Sanders, D'Amico, & Wilson, 1997). A pattern of smaller effect sizes was not observed in these latter studies, however.

Another possible source of variability concerns differences in sample sizes across studies. Sample sizes ranged from eight to 55 participants. Studies with relatively large samples (e.g., Perkins et al., 2000; Perkins, Gerlach, Broge, Grobe et al., 2001) are expected to yield a more accurate estimate of the true effect size compared with studies with small samples (Perkins et al., 1993). However, considerable variability exists in the effect sizes from studies with larger samples. For example, in Perkins et al. (2000), the placebo and low-dose effect sizes for "relaxed" for smokers were +0.27 and −0.53, respectively, whereas the corresponding effect sizes for the Perkins, Gerlach, Broge, Grobe et al. (2001) study were +0.03 and −0.35, respectively. Relatively large differences were seen for other mood measures for equivalent doses. Thus differences in sample size did not appear to account for the observed variability.

Finally, a more troubling possibility is that the variability was random. That is, intrasubject responses to nicotine may be highly variable in an unsystematic way (i.e., unpredictable) across drug administrations. To investigate this possibility, Perkins and colleagues (Perkins, Jetton, Stolinski, Fonte, & Conklin, 2004) examined the consistency of responses to a fixed dose (20 μg/kg) of nicotine across four dosing trials in a single session and across three sessions. These investigators found only a modest degree of variability across trials and across doses. Across four dosing trials within a single session (which is the procedure Perkins and colleagues follow in most of their studies of the subjective effects of nicotine), the intraclass correlations ranged from .93 for head rush to .84 for vigor. However, the intraclass correlation for trial 1 across two sessions was substantially lower; it ranged from .59 for vigor to .79 for fatigue (relaxed and tension were not assessed in this study). This result suggests that findings based on a single-dose administration may not be reliable; interestingly, all the intravenous studies used a single-dose administration. However, results of this study do not help to explain the relatively high degree of variability we found across the nasal spray studies.

Statistical power

As noted earlier, sample size in many studies affected the ability to detect statistically significant effects between doses. Only nine or ten subjects participated in studies using intravenous administration. The 11 nasal spray studies with smokers had 8–55 participants; eight of these studies included fewer than 20 participants. A power analysis revealed that a study with 10 participants has only 30% power to detect a medium effect size ($p<.05$; two-tailed α). A total of 30 participants would be needed to detect a medium effect size of .50 with a power of .80. None of the studies had sufficient power to detect a small effect size. Even with a sample of 50 participants, a study would have only about 40% power to detect a small effect of .20. Similarly, most studies using other routes of administration have been underpowered. For example, 26 studies with cigarettes have been conducted; 17 of these studies had fewer than 20 participants (see Tables 2 and 3 in Kalman, 2002). Larger samples are obviously even more important when moderator effects are the focus of interest (see below).

In addition, we investigated power in the current set of meta-analyses as a function of effect size (i.e., $d_+=.20$=small effect; $d_+=.50$=medium effect; and $d_+=.80$=large effect), number of effect sizes being combined ($k=3$ and $k=6$), and average sample size in the studies from which the individual effect sizes were drawn ($n=10$ and $n=20$). Power was computed according to methods described in Hedges and Pigott (2001). These power analyses showed that d_+ values based on combining three effect sizes from small size studies ($n=10$) were significantly underpowered to detect small and medium effect sizes (power=.12 for small effect sizes and .49 for medium effect sizes). This problem is an issue primarily for the intravenous nicotine analyses. Power for large effect sizes was adequate (.87) where $k=3$ and $n=10$. In contrast, d_+ values based on combining six effect sizes from medium-size ($n=20$) studies had good power to detect medium and large effect sizes (power=.97 and .99, respectively). However, power to detect small effect sizes was found to be low (.34) when $k=6$ and $n=20$. Based on these power analyses, the majority of nasal spray meta-analyses appear to have been adequately powered, whereas the majority of intravenous nicotine meta-analyses were underpowered.

The subjective effects of nicotine: Importance of moderator variables

Our findings suggest that head rush and drug high may partially mediate the reinforcing effects of nicotine for smokers (see also Perkins, Gerlach, Broge, Fonte et al., 2001). Little evidence from these findings indicates that nicotine reinforcement is mediated by other subjective effects. Of course, the subjective effects of nicotine delivered via smoked tobacco versus nasal spray or intravenous administration may be more pronounced, particularly because nicotine via smoked tobacco reaches the brain more quickly. In addition, the subjective effects of smoked tobacco may be influenced by conditioned reinforcers such as the sensations of smoke in the throat (Rose, Westman, Behm, Johnson, & Goldberg, 1999). However, most studies with smoked tobacco reported nonsignificant main effects (Kalman, 2002), although many of these studies also suffered from small sample sizes. Taken together, the evidence that the subjective effects of nicotine directly mediate its reinforcing effects is quite modest.

As discussed in recent reviews, moderator variables represent a potentially important model parameter for investigators to consider in studying the subjective effects of nicotine (Gilbert & Gilbert, 1998; Kalman, 2002; Kassel et al., 2003; see also Perkins, 1999). For example, as with arousal, the tension-reducing effects of nicotine may be state dependent (Perkins, 1999). That is, nicotine may be tension-reducing when stress level is high, whereas it may have little effect (or may even be anxiogenic) when stress level is low (e.g., Gilbert, Robinson, Chamberlin, & Spielberger, 1989). Studies also suggest that the subjective effects of nicotine are moderated by individual difference variables, including trait hostility, expectancies, and gender (Jamner, Shapiro, & Jarvik, 1999; Juliano & Brandon, 2002; Perkins, Jacobs, Pelayo, Sanders, & Caggiula, 2002). Kassel and Unrod (2000) found evidence for even more complex interactions. These investigators showed that smoking may have a calming or stress-relieving effect only (or especially) among highly anxious smokers and only in combination with a distracting stimulus (but see Herbert, Foulds, & Fife-Schaw, 2001). Additional studies are needed to test moderator hypotheses, and it would be useful for investigators to report the effect sizes for interactions. Finally, research suggests that nicotine self-administration may be maintained by mechanisms independent of nicotine's subjective effects, including conditioned reinforcers and neurochemical adaptations that underlie the development of drug-seeking behavior (Caggiula et al., 2001; Robinson & Berridge, 2001).

Limitations of the current meta-analyses and directions for future research

The present study was limited primarily by the number of available effects sizes. We were not able to conduct meta-analyses of studies with smoked tobacco, nicotine gum, nicotine inhaler, or the

nicotine patch. In the case of nicotine gum, inhaler, and patch, few relevant studies have been conducted. In the case of smoked tobacco, the data needed to conduct meta-analyses were unavailable either in the published articles or from the authors. Given the challenges encountered in the current set of meta-analyses, it will be important for future studies to routinely report these data or make them available to other investigators. Also, we were unable to conduct meta-analyses on several theoretically important subjective effects (e.g., depressed mood, anger) because surprisingly few studies assessed these mood states.

As discussed earlier, small sample sizes greatly limited the ability of the majority of studies to detect statistically significant effects of nicotine. Future studies would benefit from larger samples. It also will be important for future studies to incorporate conceptually and psychometrically strong measures of subjective effects. This has not always been the case. As noted earlier, the Bond–Lader measure used by Foulds et al. (1997) contains an admixture of items that do not fall into the same octant of the circumplex model. This lack of conceptual cohesion among items in a scale presumably diminishes its reliability and greatly complicates the interpretation of data. The Addiction Research Center Inventory measure used in several studies (e.g., Heishman et al., 1993; Jones, Garrett, & Griffiths, 1999; Knott, Harr, & Lusk-Mikkelsen, 1998) suffers from the same problem. More generally, investigators should include measures derived from theory-based models of affect (e.g., J. A. Russell & Feldman Barrett, 1999; Tellegen, Watson, & Clark, 1999). These measures have the additional advantage of allowing investigators to determine the effect of nicotine both on the core affective dimensions (pleasantness/unpleasantness, high arousal/low arousal) and on discrete affects (e.g., content, relaxed, depressed, tense; J. A. Russell & Feldman Barrett, 1999; Tellegen et al., 1999). A dimensional model may best capture the affective experience of some individuals, whereas a discrete model may more accurately capture the affective experience of others (Feldman Barrett & Russell, 1998). These measures have the additional advantage of including items to assess anger. As noted above, a placebo-controlled field study with the nicotine patch found that nicotine reduced reports of anger in smokers high in trait hostility (Jamner et al., 1999). Measurement of anger has been notably absent in laboratory studies of the subjective effects of nicotine.

Additional research also is needed to investigate the moderating influence of other drug dependencies (e.g., cocaine dependence) on the subjective effects of nicotine. These investigations promise to help us understand the high prevalence of nicotine dependence in this population and the difficulty these smokers have quitting. To our knowledge, only Hughes, Rose, and Callas (2000a) have investigated this issue; other studies have begun to investigate the effect of concurrent administration of other drugs on smoking reward (e.g., Rose et al., 2002). Additional research also is needed to investigate the moderating influence of other individual difference and situational variables on the subjective effects and reinforcing value of nicotine. Perhaps most important, progress in this area will depend on our ability to identify the reasons for the substantial variability across studies in the subjective effects of nicotine. Finally, the majority of placebo-controlled studies to date have focused on the main effects of nicotine. Additional research is needed to test mediator and moderator models of nicotine's subjective and reinforcing effects (e.g., Gilbert, 1995; Kassel, 1997). Such theory-driven investigations hold the greatest promise to advance our understanding of the factors that promote tobacco dependence.

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(*Note.* References marked with an asterisk were included in the meta-analyses.)

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