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Effects of nicotine in experimental animals and humans: an update on addictive properties

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Abstract

Tobacco use through cigarette smoking is the leading preventable cause of death in the developed world. Nicotine, a psychoactive component of tobacco, appears to play a major role in tobacco dependence, but reinforcing effects of nicotine have often been difficult to demonstrate directly in controlled studies with laboratory animals or human subjects. Here we update our earlier review published in *Psychopharmacology* (Berl) in 2006 on findings obtained with various procedures developed to study dependence-related behavioral effects of nicotine in experimental animals and humans. Results obtained with drug self-administration, conditioned place preference, subjective reports of nicotine effects and nicotine discrimination indicate that nicotine can function as an effective reinforcer of drug-seeking and drug-taking behavior both in experimental animals and humans under appropriate conditions. Interruption of chronic nicotine exposure produces ratings of drug withdrawal and withdrawal symptoms that may contribute to relapse. Difficulties encountered in demonstrating reinforcing effects of nicotine under some conditions, relative to other drugs of abuse, may be due to weaker primary reinforcing effects of nicotine, to aversive effects produced by nicotine, or to a more critical contribution of environmental stimuli to the maintenance of drug-seeking and drug-taking behavior with nicotine than with other drugs of abuse. Several recent reports suggest that other chemical substances inhaled along with nicotine in tobacco smoke may play a role in sustaining smoking behavior. However, conflicting results have been obtained with mice and rats and these findings have not yet been validated in non-human primates or human subjects. Taken together, these findings suggest that nicotine acts as a typical drug of abuse in experimental animals and humans under appropriate situations.

INTRODUCTION

Tobacco smoking is presently estimated to cause 20% of all deaths in developed countries. As with other types of drug dependence, tobacco dependence is described as a chronic, relapsing disorder in which compulsive drug-seeking and drug-taking behavior persist despite negative consequences and the motivation to quit. The high addictive effects of tobacco are exemplified by the great difficulty in quitting smoking. Although most smokers want to stop, only a small percent succeed. It is now becoming clear that continued tobacco use induces adaptive changes in the central nervous system that lead to drug dependence

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(American Psychiatric Association 2000). Nicotine, the major psychoactive component of tobacco, is thought to play a critical role in tobacco dependence through its actions as a reinforcer of drug-seeking and drug-taking behavior (Fiore et al. 2000; Henningfield and Goldberg 1983; Stolerman and Shoaib 1991). Nevertheless, tobacco smoke contains several hundred other chemical substances, some of which have psychoactive effects or may enhance the psychoactive effects of nicotine, and these other substances may contribute to the reinforcing effects of tobacco smoking (Fowler et al. 1996). Indeed, reinforcing effects of nicotine have often been difficult to demonstrate directly in past controlled studies with both laboratory animals and humans as experimental subjects. As a result, there has been some controversy in the literature about the validity of previous findings that nicotine can produce reinforcing effects in experimental animals or human subjects (Dar and Frenk 2002; 2004; Robinson and Pritchard 1992).

A variety of laboratory animal models are available to study the cardinal features of drug dependence (Deroche-Gamonet et al. 2004; Everitt and Robbins 2000; Goldberg 1975; Goldberg et al. 1981; Goldberg et al. 1975; Goldberg et al. 1979; Katz and Goldberg 1988; Le Foll and Goldberg 2005; Markou et al. 1993; Schindler et al. 2002; Schuster and Woods 1968; Spealman and Goldberg 1978; Vanderschuren and Everitt 2004). The effects of nicotine have been evaluated using animals models for studying the reinforcing effects of drug injections (intravenous drug self-administration and conditioned place preference (CPP) procedures), the subjective responses to administered drugs (drug discrimination), the withdrawal states, including behavioral disturbances, that are associated with abrupt termination of chronic drug exposure (smoking cessation or administration of selective antagonists after chronic exposure) and relapse phenomena (reinstatement of extinguished drug-seeking behavior induced by stress, drug-associated cues or drug priming). Most of these experimental studies have used rodents (rats and mice) as subjects, but results are available from studies using other animal species (monkeys and dogs) and human volunteers as subjects. We will first summarize the main experimental procedures used to assess these effects of nicotine and then review the preclinical and clinical findings obtained with nicotine using these procedures. Since previous review articles already provide detailed comparisons of the effects of nicotine in animals and humans (Henningfield and Goldberg 1983; Le Foll and Goldberg 2006; Rose and Corrigall 1997; Stolerman 1999), we focus here on the most recent important findings obtained with nicotine in animals and humans.

EXPERIMENTAL PROCEDURES FOR STUDYING NICOTINE'S EFFECTS

Intravenous drug self-administration: natural rewards, such as water or food, and drugs of abuse may serve as positive reinforcers under appropriate conditions. For example, to assess the reinforcing effects of food, a food-deprived animal can be placed in a sound-attenuating chamber containing stimulus lights, response levers, and a device for dispensing food pellets. Lever-pressing responses will occur with increasing frequency when they result in delivery of food pellets, which, therefore, serve as positive reinforcers under these conditions. With intravenous drug self-administration procedures, a catheter implanted in a jugular vein allows the animal to intravenously self-administer a small amount of drug by pressing a lever. The administration of drug constitutes the event that positively reinforces the lever-pressing behavior and reward is inferred if the frequency of responding subsequently increases (thus, defining reinforcement). With these behavioral procedures, stimuli such as a light or tone are often associated with delivery of the reinforcer. It has been argued that in many instances these stimuli are not neutral, but themselves have the potential to produce weak reinforcing effects and there is accumulating evidence that nicotine exposure can increase their motivational value (i.e., they may become more effective reinforcers (Chaudhri et al. 2005). These stimuli, or 'cues', can also progressively gain motivational value by Pavlovian-conditioning and associative learning processes. In either

case, environmental stimuli can acquire the ability to facilitate the maintenance of drug-seeking and drug-taking behavior and also reinstate drug-seeking behavior that has been extinguished (Arroyo et al. 1999; de Wit and Stewart 1981; Goldberg 1975; Goldberg et al. 1975; Goldberg et al. 1981; Goldberg et al. 1983; Le Foll and Goldberg 2005; Meil and See 1996; Self and Nestler 1988; Stewart 1983), and may become critical determinants of reinforcement of drug-taking behavior by nicotine administration.

Various schedules of reinforcement have been employed to study drug self-administration behavior. Two of the most commonly used are fixed-ratio and progressive-ratio schedules of intravenous drug injection. Under a fixed-ratio schedule of intravenous drug injection, the subject must make a fixed number of responses (lever press or pull or nose-poke) in order to obtain each injection of drug (e.g., 1 lever press for a fixed-ratio 1, i.e. FR1, schedule). In contrast, under a progressive-ratio schedule of intravenous drug injection, the number of responses the subject must make to obtain successive drug injections (the ratio value) increases progressively until the subject fails to make the required number of responses (Hodos 1961). The highest ratio reached before responding ceases (the “breaking point”) is thought to reflect the reinforcing effectiveness of the drug (Donny et al. 1999; Le Foll et al. 2007). Intravenous self-administration studies have repeatedly shown that most drugs considered to be addictive in humans can serve as positive reinforcers for laboratory rats and monkeys, whereas non-addictive drugs have given negative results in the great majority of cases (Balster 1992; Katz and Goldberg 1988). Once an animal has learned to intravenously self-administer a drug, the influences of drug priming, stressors or presentation of drug-associated stimuli on drug self-administration behavior or relapse to extinguished drug-seeking behavior provide useful measures for studying the behavioral aspects of drug dependence (see Shalev et al. 2002) for a review). Interestingly, nicotine self-administration has also been studied under second-order schedules of reinforcement in non-human primates (see Everitt and Robbins 2000; Schindler et al. 2002) for reviews on those schedules). In this paradigm, animals first learn to self-administer the drug intravenously. Each drug infusion is made contingent upon a response on a lever and is paired with a light stimulus which becomes the conditioned stimulus (C.S.). During acquisition of the behavior, the number of lever responses required to produce the C.S. is progressively increased, as well as the number of C.S. presentations that have to be produced before the C.S. is paired with a drug infusion. The C.S. progressively gains motivational salience and, as a conditioned reinforcer, maintains and controls drug-seeking behavior (Goldberg and Gardner 1981; Goldberg et al. 1981).

Drug-induced conditioned place preferences: another experimental animal model for exploring the reinforcing effects of drugs of abuse is the conditioned place preference (CPP) procedure. A distinctive environment (e.g., one compartment of a two- or three-compartment apparatus) is paired repeatedly with administration of a drug, and a different environment is repeatedly associated with administration of vehicle. CPP occurs when repeated administration of a drug in this particular environment results in the ability of that environment to elicit approach behavior and increased time contact (place preference) in the absence of the previously administered drug. It has been argued that CPP, like drug self-administration and a number of related phenomena, is an example of dopamine-mediated incentive learning and that the approach behavior and increased time spent by animals in a drug-paired environment can be considered a measure of drug-seeking behavior and reinforcing effects of drugs (Bardo and Bevins 2000; Le Foll and Goldberg 2005). CPP has been demonstrated for most drugs of abuse, as well as for natural reinforcers such as food. The acquisition of a drug-induced CPP is likely to be correlated with other reinforcing effects of abused drugs, whereas its expression reflects the influence on behavior of environmental stimuli previously associated with a drug's effects.

Drug discrimination: humans exposed to psychoactive drugs report characteristic subjective effects, and drug-discrimination procedures in rats and monkeys are extensively used as animal models of these subjective reports of drug effects in humans. The ability to perceive and identify the characteristic interoceptive effects of abused drugs is thought to play a critical role in drug-seeking, encouraging the development of this behavior and directing it towards one substance rather than another, on the basis of relative potencies and subjective effects (Colpaert 1999; Stolerman and Shoaib 1991). These interoceptive subjective effects of drugs are most frequently assessed in humans through the use of subject-rating scales and correlated changes in behavior are frequently assessed using performance-assessment tasks. In animals, the interoceptive effects of drugs can serve as discriminative stimuli to indicate how to obtain a reinforcer such as a food pellet or how to avoid an electric shock (Solinas et al. 2006). For example, animals can be trained under a discrete-trial schedule of food-pellet delivery or stimulus-shock termination to respond on one lever after an injection of a training dose of nicotine and on the other lever after an injection of vehicle. Once animals learn to reliably make this discrimination, the discriminative effects of different drugs or different nicotine doses can be compared and the modulation of subjective effects of nicotine by various pharmacological treatments can be measured (Le Foll and Goldberg 2004; Le Foll et al. 2005). This procedure works well with nicotine in rats (Rosecrans 1979; Stolerman 1989) (Fig. 2A), mice (Shoaib et al. 2002; Stolerman et al. 1999) and squirrel monkeys (Takada et al. 1988) and has also been used in human subjects by using nasal sprays containing either nicotine or placebo (Perkins et al. 1996).

Measurement of withdrawal disturbances: Abrupt cessation of exposure to most drugs of abuse leads to withdrawal signs and symptoms in humans (American Psychiatric Association 2000) and these can be measured in humans by reports by subjects using standardized rating scales and by reports of trained observers (Hughes et al. 1991). Animal models have been developed to evaluate the physical signs, as well as the behavioral consequences of inferred emotional disturbances following cessation of exposure to drugs of abuse. In these procedures, the animals are frequently implanted chronically with minipumps which deliver the drug continuously and cessation is produced either by the removal of the pump or by injection of specific antagonist (Malin et al. 1992; Watkins et al. 2000).

EFFECTS OF NICOTINE IN EXPERIMENTAL ANIMALS AND HUMANS

Reinforcing effects of nicotine in experimental animals

Intravenous self-administration of a psychoactive drug is generally considered to be the most direct measure of a drug's reinforcing effects. Although intravenous drug self-administration procedures generally work well with psychostimulants and opioids over a relatively wide range of conditions, the conditions under which nicotine maintains nicotine self-administration behavior appear to be more limited. There have been criticisms in the past of the experimental conditions that were used by some investigators to study the reinforcing properties of nicotine in experimental animals. Among the confounding factors cited, we can mention here the omission of controls for general activation, insufficient consideration of secondary reinforcement processes, the use of food-deprived animals or the exclusion of animals. Our recent analysis of previous published studies performed with the intravenous nicotine self-administration paradigm in non-human primates also revealed that most of these studies do not support the conclusion that nicotine, by itself and in the absence of setting conditions, can function as an effective reinforcing agent (Le Foll et al. 2007). Specific conditions, such as automatic nicotine infusions, previous self-administration of other drugs or food, or food-deprivation, were often employed to demonstrate that nicotine could maintain significant self-administration behavior in non-human primates (Le Foll et al. 2007). In addition, these studies with nicotine self-administration in non-human primates

often used experimental conditions, such as very slow injection speeds or pre-training on other drugs of abuse that may not have been optimum for demonstrating reinforcing effects of nicotine. A clear demonstration of the reinforcing effects of nicotine in non-human primates has recently been reported (Le Foll et al. 2007). This study was performed with experimentally-naïve squirrel monkeys that had no history of exposure to other drugs of abuse, no history of drug self-administration and had not been previously trained to respond for food. Due to the growing literature obtained in rodents suggesting that nicotine may act by increasing the motivational value of environmental stimuli associated with its effects, brief light stimuli were associated with each completion of the FR response requirement on both active and inactive levers. During the first week of acquisition, no preference was noted for responding on the active versus the inactive lever (percentage choice on the active lever was $49.6 \pm 9.3\%$, as expected by chance) (Fig. 1B). However, over repeated sessions the monkeys developed a strong preference for responding on the active lever compared to the inactive lever ($P < 0.01$) and responding on the inactive lever dropped to negligible levels (Fig. 1B). This shift of responding toward the nicotine-associated lever clearly demonstrates an active choice by the monkeys towards responding that leads to nicotine delivery.

Once responding was initiated, nicotine clearly maintained self-administration behavior at high levels in squirrel monkeys (Fig. 2), compared to saline vehicle. The reinforcing effects of nicotine appear to be particularly pronounced in squirrel monkeys (Le Foll et al. 2007) allowing persistent maintenance of nicotine self-administration behavior under fixed-interval (Spealman et al. 1981), second-order (Goldberg et al. 1981), fixed-ratio (Le Foll et al. 2007; Sannerud et al. 1994) and progressive-ratio (Le Foll et al. 2007) schedules of intravenous drug injection. In the second-order and progressive-ratio experiments, the monkeys pressed up to 600 times on a lever to obtain a single injection of nicotine (Goldberg et al. 1981; Le Foll et al. 2007) demonstrating the high motivational value of nicotine that had developed in those experienced animals. In contrast, rates of responding maintained by intravenous nicotine injections in rhesus monkeys and baboons have usually been quite low (Ator and Griffiths 1983; Deneau and Inoki 1967; Goldberg et al. 1981; Slifer and Balster 1985; Wakasa et al. 1995). These results suggest that there may be species differences, although other interpretations are possible since the experimental conditions were not strictly comparable (see (Le Foll et al. 2007) for a summary). Similar differences between species have also been reported in rodents. The rate of responding maintained by nicotine is higher in rats (Corrigall and Coen 1989; DeNoble and Mele 2005; Donny et al. 1995) than in mice (Martellotta et al. 1995; Paterson et al. 2003; Rasmussen and Swedberg 1998; Stolerman et al. 1999) (Fig 2A), although this might be related to the greater number of experiments that have been conducted with rats and, thus, the better information about appropriate experimental conditions that is available. Moreover, findings have not been consistent across or within studies with rats (Brower et al. 2002; Shoaib et al. 1997), where strain differences are likely (Brower et al. 2002; Shoaib et al. 1997). It should be noted that several laboratories are now reporting significant and consistent nicotine self-administration behavior in rats, findings that likely reflect the reliability of the results that could be obtained across laboratories when nicotine is used in specific conditions.

Intravenous nicotine self-administration is usually studied under conditions where availability of injections is restricted by timeout periods ranging from several seconds to several minutes between injections and with daily sessions of short duration (Corrigall and Coen 1989) or under conditions of prolonged access to nicotine (O'Dell et al. 2007; O'Dell and Koob 2007; Valentine et al. 1997). In contrast to cocaine, where intake progressively increases after prolonged access to the drug (Ahmed and Koob 1998; Paterson and Markou 2003), no escalation in intake has been found after prolonged access to nicotine (Paterson and Markou 2004), even after periods of time ranging up to two years in recent squirrel monkey experiments (Le Foll et al. 2007). Several studies suggest that rates of responding

maintained by nicotine may be less than rates of responding maintained by cocaine when the amount of work required to obtain injections is increased in animals using progressive-ratio schedules (Goldberg and Henningfield 1988; Rasmussen and Swedberg 1998; Risner and Goldberg 1983) or that speed of acquisition of self-administration behavior may be slower than that with other drugs of abuse (Shoaib et al. 1997). However, some investigators have reported similar rates of responding for nicotine and other drugs of abuse in rodents (Paterson et al. 2004; Paterson and Markou 2003) and squirrel monkeys (Le Foll et al. 2007; Sannerud et al. 1994; Spealman and Goldberg 1982). Nevertheless, existing studies that have directly compared the reinforcing effects of nicotine to those of cocaine using progressive-ratio or choice schedules in the same animals, clearly suggest that the reinforcing effects of nicotine are weaker under progressive-ratio schedules of reinforcement (Manzardo et al. 2002; Risner and Goldberg 1983) and that animals tend to prefer cocaine over nicotine, when given the access to both drugs during the same session (Manzardo et al. 2002).

The ability of nicotine to induce CPP has also been frequently studied (Fig. 2). In the CPP procedure, animals are tested in a drug-free state to determine whether they prefer an environment previously associated with the effects of nicotine as compared to an environment previously associated with effects of saline vehicle. Thus, this procedure relies on the capacity of stimuli associated with nicotine's effects to elicit approach responses and increased time spent in the environment associated with nicotine's effects and is used as a measure of reinforcing effects. Nicotine has been shown to induce CPP across a large range of doses in some experiments (Fig. 2B), but the magnitude of the effect is generally small and affected by environmental stimuli or previous handling history (Forget et al. 2005; Grabus et al. 2006; Le Foll and Goldberg 2005), suggesting that the reinforcing effects of nicotine may be weaker than those of other drugs of abuse. Nicotine also produced aversive effects at high dose in some, but not all, studies (Grabus et al. 2006; Le Foll and Goldberg 2005). It should be noted that nicotine lowers intracranial self-stimulation reward thresholds, as assessed by intracranial self-stimulation paradigm, an effect that indicates rewarding effects of nicotine in rodents (Huston-Lyons and Kornetsky 1992).

Experimental variables such as nicotine dose, handling history or environmental cues influence the reinforcing effects of nicotine both in the intravenous self-administration and the CPP procedures (Donny et al. 1998; Grabus et al. 2006; Le Foll and Goldberg 2005). It appears, for example, that adolescent rats, food-deprived animals and rats previously exposed to nicotine are more likely to acquire intravenous nicotine self-administration behavior or to develop nicotine-induced CPP, compared to rats that are not food-deprived or not previously exposed to nicotine (Adriani et al. 2003; Belluzzi et al. 2004; Corrigall and Coen 1989; Shoaib et al. 1997; Shoaib et al. 1994; Vastola et al. 2002). However, the most important variable appears to be environmental stimuli that are repeatedly associated with nicotine injection or marginally reinforcing stimuli whose effects are facilitated by nicotine exposure.

An extensive literature suggests that Pavlovian associative conditioning processes are implicated in the acquisition of motivational value by initially neutral stimuli that are repeatedly paired with the effects of drugs of abuse. In an early paper with monkeys published in 1981, it was first suggested that environmental stimuli associated with nicotine administration are critical for the maintenance of nicotine-seeking behavior (Goldberg et al. 1981). During these experiments, a light stimulus was repeatedly paired with nicotine delivery. Although responding ultimately depended on injections of nicotine, the brief light stimulus associated with injections played an important role in the maintenance of persistent responding, since rates of responding were about twice as high when the brief light was presented as when it was absent (Goldberg et al. 1981).

The critical role played by environmental stimuli in the reinforcing effects of nicotine has recently been demonstrated in rodents (see (Caggiula et al. 2002; Le Foll and Goldberg 2005) for detailed analysis). In those experiments, discontinuing presentation of environmental stimuli associated with intravenous nicotine injection decreased self-administration behavior almost as effectively as the removal of nicotine itself, indicating their critical role in sustaining drug-taking behavior (Caggiula et al. 2002; Caggiula et al. 2001; Donny et al. 2003). Moreover, in some experiments with rats (Cohen et al. 2005) and squirrel monkeys (Le Foll et al. 2007), the responding maintained by nicotine-associated light stimuli was equal to the responding maintained by nicotine itself. In addition, the contingent presentation of environmental light stimuli was able to maintain responding for prolonged period of time in rats (Cohen et al. 2005) and squirrel monkeys (Le Foll et al. 2007), demonstrating their persistent nature and their high motivational value. Finally, the use of behavioral procedures which do not have environmental stimuli directly paired with nicotine delivery has been reported to result in very low levels of drug-taking behavior in experiments with drug-naïve mice (Paterson et al. 2003) and rats (Donny et al. 2003).

Nicotine, like other psychostimulant drugs (Hill 1970), also produces unconditioned effects that increase the ability of non-drug environmental stimuli to serve as reinforcers, independently of any direct temporal association between nicotine administration and stimulus presentation (Caggiula et al. 2002; Chaudhri et al. 2006; 2007; Olausson et al. 2003; 2004; Palmatier et al. 2007; Palmatier et al. 2007). As an example, in some experiments, noncontingent nicotine, whether delivered as discrete injections based on a pattern of self-administered nicotine or as a continuous infusion, increased response rates maintained by the visual stimulus. There were no significant differences in responding by animals that received contingent compared with noncontingent nicotine when a visual stimulus was available. Interestingly, operant behavior was equally attenuated and reinstated by the removal and subsequent replacement of contingent and noncontingent nicotine. Although nicotine supported self-administration in the absence of response-contingent, nicotine-paired stimuli; however, response rates were drastically reduced compared with nicotine self-administration with the visual stimulus (Donny et al. 2003). These experiments suggest that nicotine influences operant behavior in two ways: by acting as a primary reinforcer when it is contingent upon behavior, and by directly potentiating the reinforcing properties of other stimuli through a nonassociative mechanism. It is still unclear whether both processes occur concurrently in smokers, magnifying the role of associated environmental stimuli in nicotine self-administration and tobacco dependence, or whether one process predominates. Interestingly, these conditioning processes may also occur with sensorimotor stimuli of tobacco smoke (Rose et al. 2003; Rose et al. 2000) and this could explain the reduction in subjective reports of tobacco craving, desire to smoke, and tobacco withdrawal that are produced by placebo cigarettes in smokers (Butschky et al. 1995; Robinson et al. 2000).

Reinforcing effects of nicotine in humans

Critical variables determining whether or not nicotine functions effectively as a reinforcer of drug-seeking and drug-taking behavior in the laboratory are becoming clear. In human subjects studied under controlled laboratory conditions, reliable evidence that nicotine, by itself, can serve as an effective reinforcer of drug-taking behavior has until recently been primarily indirect. For example, cigarette smoke intake varies as a function of various manipulations affecting nicotine exposure, and pure nicotine medications (nicotine replacement therapy through patch, gum, nasal spray or inhaler) can be used as temporary or long term substitutes to facilitate smoking cessation (Fiore 2000; Le Foll and George in press). However, the persistent use of nicotine replacement therapy (NRT) provides only indirect evidence for reinforcing effects of nicotine in humans, since NRT use may be

maintained by the knowledge of the subjects that it helps smoking cessation outcome. Nevertheless, in this situation, smokers will self-administer nicotine spray more than placebo over several days after quitting smoking (Perkins 2004). However, the reinforcing effects of nicotine gum in smokers are highly dependent on instructions given to them, suggesting that either pharmacological effects are not the only factors involved in the maintenance of use of NRT (Hughes 1989) or that instructions may affect the ability of the subject to derive the pharmacological effects from the gum.

An analysis of laboratory experiments evaluating self-administration of nicotine by intravenous injection or by nasal spray in human cigarette smokers concluded that clear differences between voluntary responding for nicotine injections and saline injections had not yet been demonstrated (Dar and Frenk 2004), although these conclusions have been disputed (Perkins 2004) and recent studies now clearly indicate that human smokers will self-administer nicotine intravenously (Harvey et al. 2004; Sofuoglu et al. 2007). In a recent study conducted with male cigarette smokers who had been smoking an average of 1.5 pack of cigarettes/day for an average of 13.4 years, nicotine was shown to act as an effective reinforcer of intravenous self-administration behavior (Harvey et al. 2004) (Fig. 2E–F). Before each session, a catheter was inserted in a forearm vein for delivery of nicotine or saline. During experimental sessions, subjects sat in a chair in a test room facing a test panel with two levers and a stimulus light over each lever. When the subject pulled either lever, there was an audible click and a response was recorded. Pulling one lever repeatedly produced intravenous injections of nicotine while pulling the other lever produced injections of saline. Note that each delivery of nicotine was associated with the presentation of a stimulus light. The number of lever-pull responses required to produce an injection varied between sessions from 10 to as high as 1600. As the response requirement increased, response rates on the nicotine lever increased substantially, while rates on the saline lever remained low (Fig. 2FD). The number of injections per session was markedly and significantly greater for nicotine than saline (Fig. 2E) and varied as a decreasing function of the dose of nicotine (Harvey et al. 2004). In these experiments, subjects adjusted their responding to increasing response requirements in a way that maintained relatively constant levels of nicotine injections per session. In another recent study, several doses of nicotine were preferred over placebo in a pure nicotine intravenous self-administration study in male and female cigarette smokers (Sofuoglu et al. 2007). The findings from these two studies clearly demonstrate that nicotine, by itself, in the absence of other constituents of tobacco smoke, can serve as an effective reinforcer of intravenous drug-taking behavior in human cigarette smokers.

The earlier difficulties in obtaining reliable intravenous nicotine self-administration and nicotine-induced conditioned place preferences across species and laboratories suggest that the reinforcing effects of nicotine, by itself, may be lower than the reinforcing effects of other drugs of abuse under many experimental conditions. These findings contrast with the apparently high reinforcing effects of tobacco smoke in human smokers. These discrepancies could be explained in part by different reinforcing effects of nicotine between species or by the influence of non-nicotine stimuli associated with smoking. An additional possibility is that the reinforcing properties of nicotine in tobacco smoke may be enhanced by other constituents of tobacco smoke. Recently, it has been shown that behavioral sensitization to nicotine, which has been implicated in drug dependence (Robinson and Berridge 1993; 2001), becomes long-lasting when nicotine is administered after treatment with a monoamine-oxidase inhibitor (Villegier et al. 2003), and tobacco smoke is known to contain many compounds, some of which are monoamine-oxidase inhibitors (Fowler et al. 1996; Fowler et al. 1996). Moreover, recent results obtained in rats suggest that treatment with MAO inhibitors may potentiate the reinforcing effects of intravenously self-administered nicotine (Guillem et al. 2005; 2006; Villegier et al. 2006). However,

conflicting results have been obtained in mice (Agatsuma et al. 2006) and the results obtained in rats were obtained with a degree of MAO inhibition that is much higher than that observed in the brains of smokers (Fowler et al. 1996; Fowler et al. 1996). Further studies are needed in non-human primates and human subjects to validate those findings.

Another substance that is inhaled in cigarette smoke along with nicotine is acetaldehyde. Potentiation of the effects of nicotine by acetaldehyde has also been demonstrated in rodents (Belluzzi et al. 2004), although it is unclear how this substance diffuses into the brain of smokers and how it interacts *in vivo* with brain reward circuitry. Further experiments are needed to clarify the role of these constituents of tobacco smoke in the reinforcing effects of tobacco.

Subjective effects of nicotine in humans and discriminative and aversive effects in animals

Discriminative-stimulus effects of nicotine in experimental animals—The discriminative-stimulus effects of nicotine, which are extensively used as an animal correlate of subjective reports of nicotine effects in humans, are mainly mediated by neuronal nicotinic acetylcholine receptors (nAChR), since discrimination of nicotine can be blocked by mecamylamine, a nicotinic receptor antagonist that penetrates the blood-brain barrier, but not by the nicotinic receptor antagonist hexamethonium, which does not readily enter the brain (Kumar et al. 1987; Pratt et al. 1983; Stolerman 1999; Stolerman et al. 1984). These discriminative effects are mainly mediated by high affinity nicotinic receptors (Shoaib et al. 2002; Stolerman et al. 1997). Nevertheless, a dopaminergic component may also be involved (Corrigall and Coen 1994; Desai et al. 2003; Gasior et al. 1999; Le Foll et al. 2005). The areas of the brain that appear to be most strongly implicated in the mediation of nicotine's discriminative stimulus effects are the prefrontal cortex and the ventral striatum, but the hippocampus may also be involved (Ando et al. 1993; Miyata et al. 1999; 2002; Rosecrans and Meltzer 1981). It should be noted that the discriminative-stimulus effects of nicotine may not be related to the properties of nicotine that lead to nicotine self-administration and dependence, as suggested for other psychostimulant drugs (Spealman et al. 1999).

Aversive effects of nicotine in experimental animals—It has long been known that nicotine can produce both reinforcing and aversive effects, sometimes at the same dose, depending on the experimental conditions and the subject's history (Goldberg et al. 1983; Henningfield and Goldberg 1983). In agreement, the same dose of nicotine may produce either positive or aversive motivational effects in rats using the place conditioning procedure (Laviolette and Van Der Kooy 2003; Le Foll and Goldberg 2005). Similarly, squirrel monkeys will learn to repeatedly press a lever in order to obtain intravenous injections of nicotine (Fig. 3B) (Goldberg et al. 1981). However, ongoing lever-press responding for food is completely suppressed (punished) when lever presses produce intravenous injections of the same dose of nicotine that can maintain self-administration behavior under other conditions (Fig. 3B) (Goldberg and Spealman 1983). Further, monkeys will learn to press a lever to avoid programmed injections of nicotine (Spealman 1983). Aversive effects of nicotine have also been demonstrated in rats using the conditioned taste aversion procedure with systemic nicotine injections (Reavill et al. 1986; Shoaib and Stolerman 1995; Stolerman 1988) and with intracranial infusions of nicotine (Laviolette and Van Der Kooy 2003; Shoaib and Stolerman 1995).

Discriminative-stimulus and aversive effects of nicotine in humans—Humans subjects can be trained to discriminate the effects of inhaled nicotine administered by nasal spray (Perkins et al. 1997) (Fig 3C). Interestingly, subjects reported both positive and negative effects following intravenous nicotine self-administration, although the positive

effects were more pronounced (Fig. 2E) (Harvey et al. 2004). A recent review of the literature on subjective effects of nicotine in human subjects indicated that, across various delivery forms, nicotine increased ratings of positive effects in smokers, such as high, liking, and euphoria (Kalman 2002). Studies involving intravenous nicotine administration have reported similar positive effects, but have also shown that nicotine can elicit concurrent reports of negative effects, such as tension, jitteriness, and dysphoria (Garrett and Griffiths 2001; Henningfield et al. 1985; Jones et al. 1999; Soria et al. 1996). It is likely that subjective effects and reinforcing effects of drugs of abuse can be dissociated and that drugs of abuse may function as highly effective reinforcers even when they produce measurable reports of negative effects (Ettenberg and Geist 1991). Also, drugs of abuse may continue to function as highly effective reinforcers when dose is reduced to the point that reports of positive effects are absent (Lamb et al. 1991; Panlilio et al. 2005). Interestingly, it appears that discrimination procedures in animals and humans often provide similar results (Fig. 3). As an example, recent findings indicate that ethanol does not produce nicotine-like effects in rats (Le Foll and Goldberg 2005), as shown in humans (Perkins et al. 2005).

Nicotine withdrawal signs in experimental animals—A wide range of behavioral signs (e.g., teeth chattering, chewing, gasping, writhing, head shakes, body shakes, tremors) have been noted upon cessation of chronic nicotine exposure in experimental animals (Epping-Jordan et al. 1998; Isola et al. 1999; Malin et al. 1992; Paterson and Markou 2004; Suzuki et al. 1996). Generally, rats or mice are chronically implanted with minipumps which deliver nicotine continuously and withdrawal signs are seen after either removal of the pump or injection of a nicotinic antagonist (Malin et al. 1992; Watkins et al. 2000). To monitor physical signs of withdrawal, the number of occurrences of each sign is counted and the subject's overall withdrawal score is the number of signs cumulated across all categories (Malin et al. 1992). These behavioral withdrawal signs have been termed "somatic abstinence signs" or "somatic behavioral signs".

The physical signs of nicotine withdrawal often are accompanied by behavioral disturbances, such as higher electrical thresholds for intracranial self-stimulation (ICSS), suggesting hypoactivity of brain reward pathways (Epping-Jordan et al. 1998). Interestingly, with mild nicotine withdrawal, indications of emotional disturbance are more likely to appear than are the behavioral somatic signs listed above. Nicotine withdrawal is also associated with avoidance behavior. Rats will avoid a compartment associated with mecamylamine-precipitated nicotine abstinence using a conditioned place preference procedure (Suzuki et al. 1996). Nicotine also has antidepressant-like effects in the forced-swim test (Tizabi et al. 1999; Tizabi et al. 2000) in Flinders-sensitive rats, a strain of rat that has been proposed as an animal model of depression (Overstreet 1995; Overstreet et al. 1995). The available evidence suggests that different underlying neurochemical deficits mediate somatic and affective components of nicotine withdrawal (see (Kenny and Markou 2001) for a review).

Nicotine-withdrawal signs and symptoms in humans—Tobacco withdrawal induces a wide range of signs and symptoms in human smokers (Hughes et al. 1991; Hughes and Hatsukami 1986). For tobacco users trying to quit, symptoms of withdrawal from nicotine are unpleasant and stressful, but temporary. Since nicotine replacement therapy strongly decreases the intensity of withdrawal symptoms (Hughes et al. 1984; West et al. 1984), it is assumed that the decrease in nicotine levels is responsible for the tobacco withdrawal symptoms in humans. Reducing the nicotine content of cigarettes can also result in a withdrawal syndrome (West et al. 1984), as well as ceasing the use of nicotine gum (Hughes et al. 1986; West and Russell 1985). Signs and symptoms of nicotine withdrawal include any or all of the following: headache, nausea, constipation or diarrhea, falling heart rate and blood pressure, fatigue, drowsiness and insomnia, irritability, difficulty

concentrating, anxiety, depression, increased hunger and caloric intake, increased pleasantness of the taste of sweets, and tobacco cravings. Most withdrawal signs and symptoms peak 48 hours after quitting tobacco smoking and are completely gone in six months (Le Foll et al. 2005). Slowing of heart rate and weight gain are distinguishing features of tobacco withdrawal, compared to other drugs of abuse (Hughes et al. 1994).

Interestingly, cessation of tobacco use increases the risk of depression (Glassman et al. 1990) and this vulnerability persists for several months (Glassman et al. 2001). However, it is unclear if this effect reflects an increased risk of depression or a relapse to depression. There is some evidence that nicotine itself may possess antidepressant properties in humans (Salin-Pascual and Drucker-Colin 1998; Salin-Pascual et al. 1996) (see Picciotto et al. 2002 for a review), but these results have not yet been validated in placebo-controlled clinical trials (Thorsteinsson et al. 2001). Also, tobacco smoke contains chemical substances other than nicotine that may have antidepressant effects, possibly through the prolonged inhibition of monoamine oxidase A and B in the brain (Berlin and Anthenelli 2001; Fowler et al. 1996; Fowler et al. 1996; Meyer et al. 2006). The increased risk of depression following smoking cessation may be related to factors other than nicotine. Nevertheless, withdrawal symptoms that occur following smoking cessation may contribute to difficulties in quitting smoking.

Relapse models: influence of stress, drug priming and presentation of cues

'Relapse' in experimental animals—The animal model most frequently used to study relapse phenomena is reinstatement of extinguished drug self-administration behavior (see (Epstein and Preston 2003; Katz and Higgins 2003; Shaham et al. 2003) for reviews and discussions on the limitations of the reinstatement model in animals to study relapse in humans). Only limited research has been conducted with nicotine, as compared to other drugs of abuse. Various factors thought to trigger relapse in humans appear able to reinstate nicotine-seeking in laboratory animals. Studies in rats have shown that non-contingent administration of nicotine during extinction of nicotine self-administration behavior reinstates responding previously reinforced by nicotine (Andreoli et al. 2003; Chiamulera et al. 1996; Dravolina et al. 2007; Lindblom et al. 2002; Shaham et al. 1997) (and Le Foll *et al.*, unpublished studies). However, the effect of nicotine priming is weak in some studies as compared to other drugs of abuse (Erb et al. 1996; Shaham et al. 1996) and effects are not found consistently (Lesage et al. 2004). Exposure to drug-paired stimuli also appears effective in reinstating extinguished nicotine-seeking behavior (Dravolina et al. 2007; Lesage et al. 2004; Liu et al. 2006; Liu et al. 2007) and in facilitating the reacquisition of nicotine self-administration behavior after a period of extinction (Caggiula et al. 2001). However, some investigators have found no effect of exposure to nicotine-paired stimuli on nicotine-seeking behavior (Andreoli et al. 2003). Exposure to stressors is also able to reinstate extinguished nicotine-seeking behavior (Buczek et al. 1999). Although all of these experiments are not entirely consistent (see above), it appears that extinguished nicotine-seeking behavior generally can be reinstated by all factors that are effective in reinstating extinguished cocaine- or heroin-seeking behavior.

The existing treatments available to treat human smokers (Fiore et al. 2000; Le Foll and George in press) have only recently been evaluated in animal models of nicotine dependence. The major findings are listed in Table 1. This Table also reports the results obtained with drugs that have been tested both in animals and humans (for more extensive reviews see (Cryan et al. 2003; George and O'Malley 2004). It appears that nicotine replacement therapy (LeSage et al. 2003; LeSage et al. 2002) and bupropion (Bruijnzeel and Markou 2003; Rauhut et al. 2003; Shoaib et al. 2003) are able to affect nicotine self-administration behavior, but the results have not been consistent across studies with bupropion (perhaps due to the role of bupropion metabolites in the therapeutic efficacy of

this drug). Nicotine replacement therapy and bupropion also are effective in attenuating nicotine withdrawal signs and symptoms. These drugs have not been evaluated in animal models of nicotine relapse. Varenicline (a nicotinic receptor partial agonist) is also an efficacious agent to treat tobacco dependence (Gonzales et al. 2006; Jorenby et al. 2006; Nides et al. 2006; Oncken et al. 2006; Tonstad et al. 2006) and it produces some effects on nicotine discrimination and on nicotine self-administration (Rollema et al. 2007). Recent evidence suggests that innovative approaches such as the blockade of cannabinoid CB₁ receptors (Cohen et al. 2005; Forget et al. 2005; Le Foll and Goldberg 2004; 2005) or blockade of dopamine D₃ receptors (Andreoli et al. 2003; Le Foll et al. 2005; Le Foll et al. 2003; Le Foll et al. 2005), which are over-expressed in the brain of nicotine-treated animals (Le Foll et al. 2003; Le Foll et al. 2003), decreases the influence of nicotine-associated stimuli or nicotine priming on nicotine-seeking behavior (Le Foll and Goldberg 2005; Le Foll et al. 2007).

Relapse in humans—Tobacco-seeking, craving and relapse in humans are well known to be triggered by environmental stimuli, or ‘cues’, that have acquired motivational salience through repeated associations with self-administered nicotine (O’Brien 2003; Shiffman et al. 2000; Shiffman et al. 1986), but may also be triggered by withdrawal symptoms and tobacco smoking in abstinent subjects. Nicotine replacement therapy, bupropion and varenicline, the three medications currently available for smoking cessation, are effective in increasing smoking cessation rates (i.e. decreased relapse rates) and are partly effective in reducing reports of craving for cigarettes in abstinent smokers (Jorenby 2002). Nicotine replacement therapy, bupropion and varenicline may act by attenuating tobacco withdrawal symptoms (Coe et al. 2005; Shiffman et al. 2000; Shiffman et al. 2000) (Table 1). Varenicline, the newest medication approved for the treatment of smokers (Cahill et al. 2007) is a nicotinic receptor partial agonist (Cahill et al. 2007). Through its intrinsic partial activation of $\alpha_4\beta_2$ nicotinic acetylcholine receptors, it may counteract withdrawal symptoms during smoking cessation attempts. Additionally, by competitively binding to $\alpha_4\beta_2$ nicotinic acetylcholine receptors, it may shield the smoker from nicotine-induced dopaminergic activation in the event that they smoke. Thus, varenicline may disrupt the reinforcing effects of tobacco and reduce nicotine withdrawal symptoms. Although this medication is efficacious in preventing smoking relapse (Tonstad et al. 2006), its effects on reactivity to associated with nicotine or tobacco smoking have not yet been assessed. Continuous nicotine replacement therapy by skin patches seems relatively ineffective in attenuating reports of craving produced by smoking-associated stimuli (cues) in smokers (Tiffany et al. 2000; Waters et al. 2004). Interestingly, nicotine gum has recently been shown to be efficacious in reducing cue-induced craving for cigarettes (Shiffman et al. 2003). These different effects of nicotine patches and gum may be due either to the tolerance that occurs with continuous exposure to nicotine through skin patches or to the failure to specifically evaluate effects of the skin patches in the subgroup of subjects displaying a high degree of cue-reactivity. Recent imaging studies suggest that reports of craving and brain activation induced by environmental stimuli (‘cues’) associated with tobacco smoking, are related to limbic brain areas (Brody et al. 2002; Due et al. 2002) and are reduced by bupropion (Brody et al. 2004). Rimonabant also seems effective in preventing relapse to tobacco use in abstinent smokers (Anthenelli and Despres 2004) (Table 1). Although Rimonabant appears to decrease the reactivity to nicotine-associated stimuli in animals, parallel experiments have not yet been conducted in humans.

CONCLUSIONS

In conclusion, nicotine functions as an effective reinforcer of drug-seeking and drug-taking in both humans and experimental animals. In intravenous drug self-administration studies, nicotine can serve as a prototypical drug of abuse under certain conditions, maintaining very

high levels of operant responding that are clearly distinguishable from responding maintained by saline placebo in both experimental animals and human smokers. Nicotine is also able to induce significant CPP in rodents. Thus, reinforcing effects of nicotine have now been clearly demonstrated across procedures and across different experimental species. These procedures have revealed that nicotinic acetylcholine receptors containing the α_4 and the β_2 subunits (Picciotto et al. 1998; Tapper et al. 2004), but also cannabinoid, glutamate and γ -aminobutyric acid receptors are involved in nicotine dependence processes (Le Foll and Goldberg 2005; Liechti et al. 2007; Paterson et al. 2004) (see also chapters from Dr Balfour and Collins *et al.*). Analysis of the discriminative effects of nicotine in experimental animals and reports of subjective effects of nicotine in humans reveal a complex global effect with both positive and negative components. Both the positive and negative effects of nicotine are affected by environmental conditions and the context of the experiments, factors that may explain the difficulties in obtaining reliable results with nicotine in the past.

As with other drugs of abuse, cessation of nicotine exposure induces a withdrawal syndrome that is associated with both physical and emotional signs and symptoms. Nicotine usage may be continued by some subjects to prevent or relieve these withdrawal symptoms and, perhaps, also to prevent depression that may occur following smoking cessation. As with other drugs of abuse, nicotine priming and exposure to nicotine-associated stimuli or stressors produce reinstatement or relapse, both in experimental animals and humans. Medications that are effective in humans for increasing smoking cessation rates generally appear effective in reducing intravenous nicotine self-administration, nicotine withdrawal signs and the effects on behavior of presenting nicotine-associated environmental stimuli, demonstrating again a strong analogy between responding of experimental animals and humans. All of these findings indicate that nicotine can act like a typical drug of abuse both in animals and humans. In addition, innovative pharmacological treatment approaches, such as the use of dopamine D₃ antagonists (Le Foll et al. 2005; Le Foll et al. 2000; Pak et al. 2006) or cannabinoid CB₁ antagonists (Cohen et al. 2005; Forget et al. 2005; Le Foll and Goldberg 2005), are under development and show promise of being able to selectively block relapse phenomenon.

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Figure 1. Active choice of intravenous nicotine in experimentally naive squirrel monkeys

A. Monkeys sat in chambers equipped with two levers and distinctly colored light stimuli above the levers. Completion of the response requirement (the ratio) on the active lever produced a brief two-sec presentation of a light stimulus and an intravenous injection of nicotine followed by a timeout (TO) period of 5 to 60 sec. Completion of the ratio requirement on the inactive lever resulted in presentation of a brief two-sec light stimulus of a different color but no injection. The fixed-ratio (FR) response requirement was gradually increased over successive sessions from one to ten (FR 1 to FR 10). **B.** Mean percentage choice for responding on the active lever by monkeys when they were experimentally naive (first week under a FR 1 schedule) and when they had learned to self-administer nicotine under the FR 10, TO 60 sec schedule (first week under the FR 10 schedule). * $P < 0.01$, compared to the first week of training. From (Le Foll et al. 2007).

Figure 2. Reinforcing effects of nicotine in rats (A, B), non human-primates (C, D) and humans (E, F)

A. During repeated sessions, rats learned to press a lever to self-administer intravenous injections of nicotine and light stimuli were paired with each drug infusion. Results are expressed as mean ($\pm$ SEM) of number of responses on the active and inactive lever. Responding was higher on the active lever compared to the inactive lever. From (Corrigall and Coen 1989). **B** Nicotine-induced conditioned place preferences (CPP) over a large range of doses in rats. Over repeated sessions, rats were either injected subcutaneously with nicotine and then placed in one environment, or injected with saline and placed in the other environment. In a nicotine-free state, the animal was then allowed access to both environments during a test session without injection, and the amount of time spent in each environment was recorded. From (Le Foll and Goldberg 2005). **C,D** Nicotine self-administration behavior in squirrel monkeys. Number of ratios completed on the active and inactive levers per session under fixed-ratio (**C**) and progressive-ratio (**D**) schedules are shown as a function of injection dose of nicotine ($n=5$). From (Le Foll et al. 2007). **E** Human subjects learned to respond on levers to intravenously self-administer nicotine or saline. A light stimulus was paired with each injection. The number of self-administered nicotine injections was consistently higher than the number of self-administered saline injections (**E**) and rate of responding was significantly higher for nicotine than for saline when the number of responses needed to produce an injection was high (**F**). Results are expressed as the mean ($\pm$ SEM) number of injections per session (**E**) or as a function of the number of responses required for each injection of nicotine or saline (Fixed-Ratio value) (**F**). From (Harvey et al. 2004).

Figure 3. Subjective and discriminative stimulus effects of nicotine in experimental animals (A, B) and humans (C, D)

A. Dose-effect functions for the discriminative-stimulus effects of nicotine in rats ($n = 8$) trained to discriminate 200 $\mu\text{g/kg}$ of subcutaneously administered nicotine from saline. The percentage of responses on the lever associated with nicotine administration is shown as a function of dose ($\mu\text{g/kg}$) during tests with various nicotine doses. Adapted from (Chance et al. 1977). **B.** In squirrel monkeys, intravenous injections of nicotine (10.5 $\mu\text{g/kg}$) maintain intravenous self-administration behavior (adapted from (Goldberg et al. 1981)), but also act like a punisher to suppress food-maintained behavior (adapted from (Goldberg and Spealman 1983)). **C.** Dose-effect functions for the discriminative-stimulus effects of nicotine in humans (smokers or non-smokers) trained to discriminate 20 $\mu\text{g/kg}$ nicotine administered by nasal spray from placebo spray. From (Perkins et al. 1997). **D.** Reported positive and negative effects of nicotine injections in human subjects. Mean (+SEM) ratings of positive or negative effects (in mm) after intravenous injection of nicotine or saline on a 100mm visual analog scale (VAS). *: negative ratings were significantly greater for nicotine than saline. **: positive ratings for nicotine were significantly greater than negative ratings for nicotine and significantly greater than positive ratings for saline. *, **: $P < 0.05$, from (Harvey et al. 2004).

Table 1

Summary of effects of different drugs that have been tested both in experimental animals and human smokers.

Experimental animals		Human subjects	
Nicotine			
Continuous nicotine infusion decreases intravenous nicotine self-administration in rats with 23 h/day access to nicotine (no effect on cocaine self-administration).	(LeSage et al. 2003; LeSage et al. 2002)	Increased rates of smoking cessation in controlled clinical trials using nicotine replacement therapy	(Fiore et al. 2000; Le Foll et al. 2005; Silagy et al. 2000; 2000)
Repeated nicotine administration decreases discriminative stimulus effect of nicotine in rats.	(Robinson et al. 2005)	Nicotine exposure attenuates discriminative effects of nicotine in women.	(Perkins et al. 2001)
Nicotine withdrawal after chronic exposure through osmotic pumps or intravenous self-administration produces withdrawal symptoms.	(Epping-Jordan et al. 1998; Malin et al. 1992; Paterson and Markou 2004)	Nicotine replacement therapy attenuates nicotine withdrawal symptoms.	(Hughes et al. 1984; West et al. 1984),
Bupropion			
Bupropion at low doses (10–30 mg/kg) had no effect or increased intravenous self-administration of nicotine, whereas higher dose of bupropion (30–78 mg/kg) decreased nicotine self-administration under a fixed ratio schedule. Bupropion (20–40 mg/kg) had no effect on intravenous self-administration of nicotine under a progressive-ratio schedule.	(Bruijnzeel and Markou 2003; Rauhut et al. 2003; Shoaib et al. 2003)	Bupropion increased smoking cessation rate in controlled clinical trials	(Fiore et al. 2000; Le Foll et al. 2005; Tashkin et al. 2001)
Bupropion produced nicotine-like discriminative effects in two out of three studies.	(Shoaib et al. 2003; Wiley et al. 2002; Young and Glennon 2002).	Bupropion decreased reports of craving and reactivity to nicotine associated stimuli. withdrawal symptoms	(Brody et al. 2004; Hurt et al. 1997; Jorenby et al. 1999; Shiffman et al. 2000)
Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat.	(Cryan et al. 2003)	Bupropion decreased tobacco withdrawal symptoms	(Brody et al. 2004; Hurt et al. 1997; Jorenby et al. 1999; Shiffman et al. 2000)
Rimonabant (cannabinoid CB₁ antagonist)			
Rimonabant decreased intravenous self-administration of nicotine under a fixed-ratio schedule; decreased responding by nicotine-associated stimuli and blocked nicotine-induced conditioned place preference in rats.	(Cohen et al. 2005; Cohen et al. 2002; Forget et al. 2006; Forget et al. 2005)	Rimonabant increased rate of smoking cessation in the STRATUS-US trial.	(Anthenelli and Despres 2004)
Rimonabant did not produce nicotine-like discriminative stimulus effects and did not alter the discriminative stimulus effects of nicotine	(Cohen et al. 2002; Le Foll and Goldberg 2004)	Subjective effects of rimonabant are rated identical as those of placebo	(Huestis et al. 2001)
Varenicline (a nicotinic receptor partial agonist)			
Varenicline blocks the discriminative stimulus effect of nicotine and dopamine-releasing effect of nicotine. varenicline reduces nicotine self-administration in rats and supports lower self-administration break points than nicotine.	(Rollema et al. 2007)	Varenicline increases smoking cessation rates in smoking cessation trials and appear to prevent relapse.	(Gonzales et al. 2006; Jorenby et al. 2006; Nides et al. 2006; Oncken et al. 2006; Tonstad et al. 2006)
Mecamylamine (a nicotinic receptor antagonist)			
Mecamylamine decreased intravenous nicotine self-administration under various procedure in rats and monkeys	(Goldberg et al. 1981, Corrigan and Coen 1989, Donny et al. 1999)	Although acute mecamylamine increases nicotine self-administration and smoking, prolonged mecamylamine treatment has shown some interest for smoking cessation.	(Pomerleau et al. 1987; Rose et al. 2001; Rose et al. 2003))

Experimental animals		Human subjects	
Nicotine			
Mecamylamine blocks the discriminative stimulus effect of nicotine in rats	(Stolerman et al. 1997)	Mecamylamine blocks the discriminative stimulus effect of nicotine in humans	(Perkins et al. 1999; Rose et al. 1989)
Mecamylamine produces a withdrawal symptoms in rats chronically exposed to nicotine	(Epping-Jordan et al. 1998; Malin et al. 1992; Paterson and Markou 2004)	Mecamylamine produces some withdrawal symptoms in smokers	(Rose et al. 2001)