Original Investigation

Varenicline Dose Dependently Enhances Responding for Nonpharmacological Reinforcers and Attenuates the Reinforcement-Enhancing Effects of Nicotine

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Abstract

Introduction: Varenicline (VAR), a partial nicotinic agonist, is one of the most effective smoking cessation pharmacotherapies. The therapeutic efficacy of VAR could be partly the result of substituting for and/or blocking the reinforcement-enhancing effects of nicotine (NIC). We assessed the effects of VAR alone and in combination with NIC (0.4 mg/kg) while rats pressed the lever for a moderately reinforcing visual stimulus (VS).

Methods: Rats were injected with placebo (0.9% saline), NIC, VAR (0.1–1 mg/kg), or NIC + VAR. A follow-up study was conducted with a broader dose range of VAR-alone dosages (0.01–3.0 mg/kg). All drug manipulations were conducted in a between-subjects design to prevent confounding effects of repeated exposure.

Results: There was a dose-dependent effect of VAR alone. Moderate doses of VAR (0.1 and 1.0 mg/kg) increased the number of VS presentations earned, while lower and higher VAR doses (0.01 and 3.0 mg/kg) did not change responding for the VS. VAR dose dependently attenuated the reinforcement-enhancing effects of NIC, with the highest dose (1.0 mg/kg) exhibiting the greatest antagonist effect.

Conclusions: The results of these studies support the assertion that the therapeutic efficacy of VAR may be due to the partial agonist characteristics of the drug, specifically, its ability to partially replace the reinforcement-enhancing effects of NIC as well as antagonize these effects.

Introduction

Tobacco use is currently the leading cause of preventable disease and premature death in the United States (Centers for Disease

Control and Prevention, 2009). Despite the impact tobacco use has on those who smoke, quit rates are very low (Haas, Munoz, Humfleet, Reus, & Hall, 2004). Varenicline (Chantix) is currently the most efficacious pharmacotherapy for smoking cessation; however, most individuals continue to relapse (Aubin et al., 2008; Gonzales et al., 2006; Jorenby et al., 2006). It is therefore important to obtain a better understanding of the neuropharmacological and behavioral effects of varenicline; doing so could potentially lead to the development of novel smoking cessation aids and/or an increase in the effectiveness of existing medications, including varenicline.

Nicotine is presumed to be the key pharmacological agent in cigarettes that drives tobacco use (Department of Health and Human Services, Public Health Services, 1988). Despite extensive research, the behavioral, pharmacological, and biological processes underlying nicotine use remain elusive (Dani & Harris, 2005). Although nicotine acts as a primary reinforcer (i.e., behaviors leading to nicotine delivery are strengthened), these reinforcing properties are relatively weak in comparison with other highly addictive drugs of abuse. An additional mechanism that may contribute to nicotine use is the ability of nicotine to enhance the reinforcing value of both conditioned and unconditioned stimuli (i.e., reinforcement enhancement; Donny et al., 2003). The “Dual Reinforcement” model of nicotine reinforcement incorporates these two actions of nicotine (Caggiula et al., 2009).

There are currently a number of smoking cessation aids on the market, including nicotine replacement therapy (patch, lozenge, etc.), denicotinized cigarettes, and sustained-release bupropion (Zyban), but quit success rates are quite low, and relapse is common among these forms of cessation therapy (Cahill, Stead, & Lancaster, 2008; Hughes, Stead, & Lancaster, 2007; Stead, Perera, Bullen, Mant, & Lancaster, 2008). The most recently released smoking cessation aid, varenicline (Chantix), is the most effective

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smoking cessation pharmacotherapy to date. For example, varenicline reduced craving and symptoms of withdrawal significantly more than bupropion in a clinical trial (Gonzales et al., 2006) and was more effective than nicotine replacement therapy during a cessation period (Aubin et al., 2008). Those in this study who did not remain abstinent but continued to take varenicline reported decreased pleasure in smoking compared with those who did not remain abstinent but continued to receive nicotine replacement therapy. Additionally, the abuse liability of varenicline is very low, with the highest therapeutic dose (3 mg) being similar to the abuse liability of placebo (McColl et al., 2008).

Data suggest that the therapeutic efficacy of varenicline is due to its ability to substitute for and/or block the effects of nicotine on brain reward systems (Rollema, Coe, et al., 2007). These effects depend on partial agonism of $\alpha 4\beta 2$ nicotinic acetylcholine receptors (nAChRs) in midbrain reward systems (Foulds, 2006; Mihalak, Carroll, & Luetje, 2006; Rollema, Coe, et al., 2007). Thus, low to moderate doses of varenicline mimic the action of nicotine at nAChRs, while higher doses inhibit the effects of nicotine. A recent study investigated this hypothesis by looking at brain stimulation reward (BSR) threshold in rats (Spiller et al., 2009). Both nicotine (0.25 and 0.5 mg/kg) and low doses of varenicline (0.03, 0.1, and 0.3 mg/kg) reduced BSR threshold, while higher varenicline doses (3.0 mg/kg) increased BSR thresholds. Combining nicotine (0.25 and 0.5 mg/kg) with varenicline (0.3 and 1.0 mg/kg) reduced BSR thresholds relative to nicotine alone. Mecamylamine, an antagonist at non- $\alpha 7$ nAChRs, and dihydro- β -erythroidine, an antagonist at $\alpha 4$ nAChRs, blocked the enhancement of BSR seen with 1.0 mg/kg varenicline, but this effect was not blocked by methyllycaconitine, an antagonist at $\alpha 7$ nAChRs. The authors concluded that reward function (i.e., BSR threshold) is enhanced when varenicline is given in isolation at lower doses and decreased when varenicline is given at higher doses in combination with nicotine. The results from this study also demonstrated that at 1.0 mg/kg varenicline, the decrease in BSR threshold is mediated through $\alpha 4$ -containing nAChRs and not $\alpha 7$ nAChRs.

Given the partial agonist properties of varenicline and previous findings related to its rewarding effects, we sought to further investigate whether varenicline alone can noncontingently enhance operant responding for an unconditioned reinforcer and whether larger doses of varenicline can attenuate the reinforcement-enhancing effects of nicotine. To do so, we used a moderately reinforcing visual stimulus (VS), which has reliably demonstrated an increase in operant behavior when present and a significant reduction in behavior when not present (Donny et al., 2003). Two studies were conducted. Experiment 1 addressed both possibilities by assessing the effects of varenicline alone and in combination with nicotine while rats lever pressed for the VS. Experiment 2 exclusively addressed the reinforcement-enhancing effects of varenicline across a broader range of doses than Experiment 1. This was done to validate that the doses used in Experiment 1 were adequate enough to engender maximum enhancement.

Methods

General Method

Subjects

Both studies used male Sprague–Dawley rats (Harlan Farms, Indianapolis, IN). Upon arrival to the laboratory, all rats

weighed between 200 and 225 g. Rats were singly housed in hanging mesh wire cages in a colony room that was temperature controlled between 68 °F and 70 °F. Animals were on a reverse 12-hr light/dark cycle with lights off from 7 a.m. to 7 p.m. There was unlimited access to water. Unrestricted chow was provided for the first week after arrival, and the animals were handled and weighed on a daily basis. Following this period, food was restricted to 15 g/day for 1 week while animals continued to be weighed and underwent habituation and training in the operant chambers. After training was complete, diets were restricted to 20 g/day (Donny, Caggiula, Knopf, & Brown, 1995).

Apparatus

Experimental testing took place in 15 operant conditioning chambers. The chamber dimensions were 25 × 31 × 28 cm for the width, length, and height, respectively. There were two retractable levers on one wall, located approximately 2 cm from the floor of the chamber. A food pellet dispenser and trough was located between the two levers and was also approximately 2 cm from the floor of the chamber. There was a houselight on the same wall, approximately 1 cm from the ceiling of the chamber. A white stimulus light was located above both levers but was only activated above the assigned active lever as part of the moderately reinforcing VS (Palmatier et al., 2007). Additional details for the VS are described below in “Procedures.”

Drugs

Nicotine hydrogen tartrate salt (Sigma, St. Louis, MO) and varenicline (donated by Pfizer Inc.) were dissolved in 0.9% saline. The dose of nicotine used for injections was 0.4 mg/kg (reported as free base), and the solution was adjusted to 7.0 (±0.2) pH with NaOH. The doses of varenicline used for injections in Experiment 1 were 0.3, 1.0, and 3.0 mg/kg and in Experiment 2 were 0.01, 0.1, 1.0, and 3.0 mg/kg. Doses of varenicline (reported as free base) were based on previous studies (Spiller et al., 2009). The varenicline solutions were also adjusted to a 7.0 (±0.2) pH level with NaOH. All solutions were sterilized by being passed through a 0.22- μ m filter. Injections were delivered subcutaneously (SC) and intraperitoneally (IP) at a volume of 1 ml/kg.

Procedures

The following procedures follow the standard methodology used in our laboratory with a few minor training adjustments (Palmatier et al., 2006).

Habituation. Animals were placed into the operant chambers for a 20-min habituation period before training began. During this period, levers were retracted. Houselights were on while in the chamber but were illuminated red to limit visibility. Swivel attachments were placed on top of the chambers.

Magazine Training. Following habituation to the chambers, rats went through 2 days of magazine training in which the association between the sound of the food dispenser and the delivery of food was established. Animals were placed in the chamber for approximately 1 hr, and food pellets were delivered approximately every minute (i.e., 45–75 s) for a total of 60 pellets. The levers were retracted, and the houselight remained on throughout the session but was illuminated red.

Autoshaping. There were two autoshaping programs over the course of 4 successive days (2 days of the first autoshaping program followed by 2 days of the second autoshaping program).

The first autoshaping program consisted of a 1-hr session in which rats received randomized 15-s extensions of each lever, followed immediately by delivery of one food pellet. Pressing the lever during the 15-s extension resulted in the delivery of two pellets. During the second autoshaping program, rats received randomized extensions of each lever, and the rats needed to press the lever to end the trial and receive a food pellet. Rats that received ≤ 30 pellets were handshaped to press both levers at the end of the first day. All rats then completed a second day of this autoshaping program to ensure that those rats that handshaped were able to receive ≥ 30 pellets within the 1-hr session. During both autoshaping programs, the houselights were illuminated red.

Preference Assessment. All animals were exposed to a one-session preference assessment. The session began on a fixed ratio (FR) 1 schedule of reinforcement and alternated with an extinction component for the remainder of the session. Preference was determined by the animals' response allocation during the extinction period and was defined as a greater than 50% response allocation for one lever.

The experimental schedules described below are presented in Table 1.

Experiment 1

Acquisition Phase

In order to establish stable responding for the subsequent drug pretreatment phase, each animal was placed in an operant chamber and allowed to respond for the VS. The VS is established in our laboratory as a stimulus that maintains increased operant behavior, and this behavior is strongly enhanced when nicotine is simultaneously present (Donny et al., 2003). The VS consisted of illuminating the stimulus light located above the assigned active lever for 1 s and offset of the houselight for 1 min. During this 1-min period, active lever pressing had no consequence (i.e., a time-out period). Responses on the inactive lever had no consequence throughout the session. Responding was reinforced under an FR1 for one session followed by 18 FR2 sessions. On the last 5 days of the FR2 schedule, rats received both an IP saline injection 60 min prior to each session and an SC injection of saline 5 min prior to each session to habituate them to the injection procedures.

Nicotine and Varenicline Drug Pretreatment

After the acquisition phase, when stable (i.e., no increasing or decreasing trends) responding was established on an FR2, rats began the drug pretreatment phase. Animals ($n = 9$) were assigned to one of eight groups, balanced for initial lever preference. The groups were as follows: saline (SAL), 0.4 mg/kg nicotine (NIC), 0.1 mg/kg varenicline (VAR [0.1]), 0.3 mg/kg varenicline (VAR [0.3]), 1.0 mg/kg varenicline (VAR [1.0]),

0.4 mg/kg nicotine + 0.1 mg/kg varenicline (VAR [0.1] + NIC), 0.4 mg/kg nicotine + 0.3 mg/kg varenicline (VAR [0.3] + NIC), and 0.4 mg/kg nicotine + 1.0 mg/kg varenicline (VAR [1.0] + NIC). Rats receiving nicotine and saline were SC injected with the drug 5 min before each session, in addition to receiving an IP injection of saline 60 min before each session. Rats pretreated with varenicline received an IP injection of the drug 60 min prior to the session, as well as a saline or nicotine injection 5 min before the session. The injection times for nicotine and varenicline were based off of the behavioral time courses of previous studies that also focused on the reward function of each drug (Palmatier et al., 2007; Spiller et al., 2009). Groups were exposed to an FR2 schedule of reinforcement for fourteen 1-hr sessions, followed by eight 1-hr progressive ratio (PR) sessions. Longer PR sessions were not feasible due to time and chamber constraints.

Experiment 2

Acquisition Phase

Procedures were identical to Experiment 1, except that acquisition was truncated at 16 days due to stable responding.

Nicotine and Varenicline Drug Pretreatment

Procedures were identical to Experiment 1, except that there were six groups, none of which received both nicotine and varenicline. The groups were as follows: saline only, 0.4 mg/kg nicotine only, 0.01 mg/kg varenicline only, 0.1 mg/kg varenicline only, 1.0 mg/kg varenicline only, and 3.0 mg/kg varenicline only. The injection protocol was slightly different than Experiment 1 in that rats receiving nicotine were only SC injected 5 min before each session, and rats pretreated with varenicline or saline only received an IP injection of the drug 60 min prior to the session. Groups were exposed to an FR2 schedule of reinforcement for fourteen 1-hr sessions, followed by eight sessions of a 1-hr PR schedule of reinforcement.

Data Analyses

Number of VS presentations earned was the primary dependent variable. Data were analyzed using analyses of variance (ANOVAs). The first 14 sessions of drug pretreatment in both experiments (i.e., FR2) were split into two separate analyses due to response rates stabilizing during the first week of drug pretreatment. For the first seven sessions under an FR2, a two-way repeated measures ANOVA was conducted to take into account the linear effect of session and group. The same analysis was then conducted for the last seven sessions under an FR2. VS presentations were averaged for each group across all eight sessions of the 1-hr PR. Planned pairwise comparisons focused on the effects of varenicline/nicotine relative to saline and the effects of varenicline + nicotine relative to nicotine alone. Alpha was set at .05.

Table 1. Experimental Schedules

Experiment 1		Experiment 2	
Acquisition	Drug pretreatment	Acquisition	Drug pretreatment
FR1: Sessions 1–19	FR2: Sessions 20–33	FR1: Sessions 1–16	FR2: Sessions 17–30
	1-hr PR: Sessions 34–41		1-hr PR: Sessions 31–38
	3-hr PR: Session 42		

Results

Experiment 1

Acquisition Phase (19 sessions)

Active lever responding was not significantly higher than inactive lever responding on the first session of an FR1 schedule of reinforcement ($p = .24$; active mean = 74.72, $SEM = \pm 3.6$; inactive mean = 69.24, $SEM = \pm 2.96$) but was for the remainder of the acquisition phase on an FR2 schedule of reinforcement (main effect of lever on an FR2 schedule, $p < .001$; active mean on last session = 41.4, $SEM = \pm 3.91$; inactive mean on last session = 4.36, $SEM = \pm 0.52$). These differences demonstrate the primary reinforcing properties of the VS as we have previously described (Donny et al., 2003).

Nicotine and Varenicline Drug Pretreatment (23 sessions)

The effects of varenicline emerged during the first seven sessions. Statistical analyses revealed that the number of VS presentations increased linearly with session, $F(1, 58) = 28.09$, $p < .001$, and there was a significant interaction between group and the linear change over sessions, that is, a Session $\times$ Group interaction, $F(7, 58) = 2.79$, $p < .05$. Relative to the saline group, VS presentations increased linearly in the NIC ($p < .001$), VAR (0.1) + NIC ($p = 0.01$), VAR (0.3) + NIC ($p < 0.05$), VAR (1.0) + NIC ($p < .05$), and VAR (1.0; $p < .05$) groups.

Mean VS presentations of the last seven sessions for each group under an FR2 are displayed in Figure 1a. There was a dose-dependent effect of varenicline. VS presentations following the smallest dose of varenicline were high and similar to nicotine, while the largest dose of varenicline attenuated the effects of nicotine and produced responding most similar to saline. These results demonstrate varenicline's ability to mimic the reinforcement-enhancing effects of nicotine at lower doses, as well as partially block these same effects of nicotine at higher doses. A two-way ANOVA showed a significant linear session effect, $F(1, 58) = 4.55$, $p < .05$. The linear session by group interaction was not significant, indicating stable differences among the groups. Pairwise comparisons revealed that NIC, VAR (0.1), and VAR (0.3) had a significant increase in VS presentations relative to saline, while VAR (0.3) and VAR (1.0) significantly attenuated the effects of NIC.

Mean VS presentations for the eight 1-hr PR sessions are displayed in Figure 1b and demonstrate a similar pattern of what was seen under an FR2. Lower doses of varenicline produced reinforcement-enhancing effects analogous to nicotine, and higher doses of varenicline partially blocked these effects of nicotine. A two-way ANOVA demonstrated a significant linear session effect $F(1, 59) = 4.69$, $p < .05$, across the eight sessions but no interaction. Pairwise comparisons again revealed that NIC, VAR (0.1), and VAR (0.3) significantly increased VS presentations relative to saline, while VAR (0.3) and VAR (1.0) significantly attenuated the effects of NIC.

Experiment 2

Acquisition Phase (16 sessions)

Active lever responding was not significantly higher than inactive lever responding on the first session of an FR1 schedule of reinforcement ($p = .16$; active mean = 61.27, $SEM = \pm 4.55$; inactive

Figure 1. Experiment 1—Mean number of VS presentations earned following treatment with saline, nicotine only, varenicline only, or varenicline + nicotine over (a) the last 7 days of testing on an FR2 and (b) 8 days of testing on a 1-hr PR. *indicates significant difference from saline; # indicates significant difference from nicotine ($p < .05$). Varenicline alone dose dependently increased responding for the moderately reinforcing stimulus and dose dependently decreased responding compared with nicotine alone in the varenicline + nicotine groups.

mean = 53.27, $SEM = \pm 3.41$) but was for the remainder of the acquisition phase on an FR2 schedule of reinforcement (main effect of lever on an FR2 schedule, $p < .001$; active mean on last session = 41.72, $SEM = \pm 4.27$; inactive mean on last session = 5.08, $SEM = \pm 0.85$). These results further support the primary reinforcing properties of the VS.

Nicotine and Varenicline Drug Pretreatment (22 sessions)

Similar to what was seen in Experiment 1, the effects of varenicline emerged during the first seven sessions. Statistical analyses again revealed that the number of VS presentations increased linearly with session $F(1, 54) = 52.13$, $p < .001$, and there was a significant interaction between group and the linear change over sessions, that is, a Session $\times$ Group interaction, $F(5, 54) = 3.23$, $p < .05$. These results further indicated an increase in VS presentations over time, and this effect was again dependent upon group.

Relative to the saline group, VS presentations only increased linearly in the NIC group ($p < .05$).

Mean VS presentations during the last seven sessions for each group are displayed in Figure 2a. As was seen in Experiment 1, varenicline produced dose-dependent effects. The two middle doses demonstrated reinforcement-enhancing effects similar to nicotine but to a lesser magnitude, and as the dose increased and decreased, this effect diminished. A two-way ANOVA revealed a significant linear session effect, $F(1, 54) = 12.12, p = .001$, during the last seven sessions under an FR2, but the linear session by group interaction was not significant.

Mean VS presentations across the eight PR sessions are displayed in Figure 2b and corroborate the findings from an FR2. The two middle doses of varenicline displayed analogous reinforcement-enhancing effects in comparison with nicotine, and as these doses increased and decreased, the effects subsided. A two-way ANOVA demonstrated a significant linear session effect, $F(1, 53) = 8.29, p < .01$, but no interaction. Pairwise

comparisons revealed that NIC, VAR (0.1), and VAR (1.0) had a significant increase in VS presentations relative to saline.

Discussion

The aims of this study were to examine the potential reinforcement-enhancing effects of varenicline and determine whether varenicline inhibits the reinforcement-enhancing effect of nicotine. It was hypothesized that lower doses would produce a reinforcement-enhancing effect similar to nicotine and that higher doses would also block the reinforcement-enhancing effect of nicotine. These hypotheses were supported across both studies. The results of Experiment 1 indicate that a low dose of varenicline (0.1 mg/kg) has reinforcement-enhancing effects comparable to those of nicotine, and a larger dose of varenicline (1.0 mg/kg) inhibits the reinforcement-enhancing effects of nicotine. Experiment 2 extends these findings to a broader dose range, demonstrating that 0.01 and 3.0 mg/kg varenicline do not engender a reinforcement-enhancing effect, whereas 0.1 and 1.0 mg/kg do. These findings support the assertion that the therapeutic efficacy may be, in part, due to varenicline both inhibiting and replacing the actions of nicotine on brain reward function (Spiller et al., 2009).

It is interesting that larger doses of varenicline failed to affect responding for the VS. Spiller et al. (2009) reported that 3 mg/kg resulted in an increase in BSR threshold, although it is unclear why this increase occurred. The authors speculated that it was due to the larger dose producing aversive effects, similar to what is seen with higher doses of nicotine (Fudala & Iwamoto, 1986; Fudala, Teoh, & Iwamoto, 1985; Laviolette & van der Kooy, 2003; Picciotto, 2003).

Additionally, it is worth noting that 1.0 mg/kg varenicline demonstrated significant reinforcement enhancement compared with saline in Experiment 2 but not in Experiment 1. These differences are likely the result of small variations in the dose-response curve across cohorts of animals. More importantly, the shape of the curve was similar across studies with large doses being less likely to increase responding for the VS.

The two schedules of reinforcement engendered similar data across Experiments 1 and 2. Previous studies have reported divergent reports across these two schedules of reinforcement and emphasized that a PR schedule can be more sensitive to changes in reinforcer efficacy and less affected by rate-limiting or satiating effects of repeated reinforcement (Carroll, Batulis, Landry, & Morgan, 2005; Stafford, LeSage, & Glowa, 1998). The increases in behavior observed here under both schedules of reinforcement support the interpretation that varenicline increases the reinforcing efficacy of the VS.

One limitation of these studies is the use of nicotine-naïve rats as opposed to rats that are chronically exposed to nicotine. Prior research suggests that repeated exposure to nicotine leads to neuronal adaptations, including desensitization and upregulation of nAChRs (Quick & Lester, 2002). It is also believed that chronic nicotine administration engenders tolerance to most of the drug's pharmacological effects (Benowitz, 2008). Varenicline is a pharmacotherapy that is targeted toward a population that is chronically exposed to nicotine and was designed to aid smoking cessation for this group. It is therefore important to utilize a similar paradigm in an animal model, that is, a model that incorporates the neuroadaptations that occur with chronic nicotine exposure.

Figure 2. Experiment 2—Mean number of VS presentations earned following treatment with saline, nicotine only, or varenicline over (a) the last 7 days of testing on an FR2 and (b) 8 days of testing on a 1-hr PR. *indicates significant difference from SAL ($p < .05$). Varenicline alone dose dependently increased responding for the moderately reinforcing stimulus.

Another possible future direction to take includes utilizing an animal's, self-administration paradigm. To date, a limited number of studies have been conducted looking at varenicline self-administration (Rollema, Chambers, et al., 2007 and Paterson et al., 2010). These studies found that animals will self-administer varenicline but did not dissociate whether this effect was due to the primary reinforcing and/or reinforcement-enhancing effects of varenicline. Future studies should isolate the primary reinforcing effects from reinforcement enhancement in order to address the extent to which primary reinforcement is playing a role in varenicline self-administration.

Despite the known adverse health outcomes of smoking, prevalence remains high (Centers for Disease Control and Prevention 2009). As stated above, previous research suggests this may be, in part, due to the reinforcement-enhancing properties of nicotine. Our data demonstrate that varenicline independently mimics these properties as well as antagonizes them when nicotine is concurrently present. Thus, the efficacy of varenicline may be related to reinforcement enhancement in that varenicline can partially replace some of the reinforcement-enhancing effects of nicotine when a person refrains from smoking as well as hinder these effects when a person does smoke. It is crucial to better understand the mechanisms underlying these properties of nicotine and the role of smoking cessation pharmacotherapies in replacing or reducing these effects. This approach may lead to ways to improve current smoking cessation aids, such as varenicline, and/or develop novel pharmacotherapies.

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Declaration of Interests

None declared.

References

Aubin, H. J., Bobak, A., Britton, J. R., Oncken, C., Billing, C. B., Gong, J., et al. (2008). Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomized, open-label trial. *Thorax*, 63, 717–724. doi:10.1136/thx.2007.090647

Benowitz, N. L. (2008). Clinical pharmacology of nicotine: Implications for understanding, preventing, and treating tobacco addiction. *Clinical Pharmacology & Therapeutics*, 83, 531–541. doi:10.1038/clpt.2008.3

Caggiula, A. R., Donny, E. C., Palmatier, M. I., Xiu, L., Chaudhri, N., & Sved, A. F. (2009). The role of nicotine in smoking: A dual-reinforcement model. *Nebraska Symposium on Motivation*, 55, 1–19. doi:10.1007/978-0-387-78748-0_6

Cahill, K., Stead, L. F., & Lancaster, T. (2008). Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Review*, (3), CD006103.

Carroll, M. E., Batulis, D. K., Landry, K. L., & Morgan, A. D. (2005). Sex differences in the escalation of oral phencyclidine (PCP) self-administration under FR and PR schedules in rhesus monkeys. *Psychopharmacology*, 180, 414–426. doi:10.1007/s00213-005-2182-x

Centers for Disease Control and Prevention. (2009). *Targeting tobacco use: The nation's leading cause of preventable death, 2007* (Vol. 51, pp. 300–303). Washington, DC: U.S. Department of Health and Human Services.

Dani, J. A., & Harris, R. A. (2005). Nicotine addiction and comorbidity with alcohol abuse and mental illness. *Nature Neuroscience*, 8, 1465–1470. doi:10.1038/nn1580

Department of Health and Human Services, Public Health Services. (1988). *The health consequences of smoking: Nicotine addiction. A report of the Surgeon General*. DHHS (CDC) Publication No. 88–8406. Washington, DC: Government Printing Office.

Donny, E. C., Caggiula, A. R., Knopf, S., & Brown, C. (1995). Nicotine self-administration in rats. *Psychopharmacology*, 122, 390–394. doi:10.1007/BF02246272

Donny, E. C., Chaudhri, N., Caggiula, A. R., Evans-Martin, F. F., Booth, S., Gharib, M. A., et al. (2003). Operant responding for a visual reinforcer in rats is enhanced by noncontingent nicotine: Implications for nicotine self-administration and reinforcement. *Psychopharmacology*, 169, 68–76. doi:10.1007/s00213-003-1473-3

Foulds, J. (2006). The neurobiological basis for partial agonist treatment of nicotine dependence: Varenicline. *International Journal of Clinical Practice*, 60, 571–576. doi:10.1111/j.1368-5031.2006.00955.x

Fudala, P. J., & Iwamoto, E. T. (1986). Further studies on nicotine-induced conditioned place preference in the rat. *Pharmacology, Biochemistry and Behavior*, 25, 1041–1049. doi:10.1016/0091-3057(86)90083-3

Fudala, P. J., Teoh, K. W., & Iwamoto, E. T. (1985). Pharmacological characterization of nicotine-induced conditioned place preference. *Pharmacology, Biochemistry and Behavior*, 22, 237–241. doi:10.1016/0091-3057(85)90384-3

Gonzales, D., Rennard, S. I., Nides, M., Oncken, C., Azoulay, S., Billing, C. B., et al. (2006). Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: A randomized controlled trial. *Journal of the American Medical Association*, 296, 47–55. doi:10.1001/jama.296.1.47

Haas, A. L., Munoz, R. F., Humfleet, G. L., Reus, V. I., & Hall, S. M. (2004). Influences of mood, depression history, and treatment modality on outcomes in smoking cessation. *Journal of Consulting and Clinical Psychology*, 72, 563–570. doi:10.1037/0022-006X.72.4.563

Hughes, J. R., Stead, L. F., & Lancaster, T. (2007). Antidepressants for smoking cessation. *Cochrane Database of Systematic Review*, (1). doi:10.1002/14651858.CD000031.pub3

Jorenby, D. E., Hays, J. T., Rigotti, N. A., Azoulay, S., Watsky, E. J., Williams, K. E., et al. (2006). Efficacy of varenicline, an alpha4beta2

nicotinic acetylcholine receptor partial agonist vs sustained-release bupropion and placebo for smoking cessation: A randomized controlled trial. *Journal of the American Medical Association*, 296, 56–63. doi:10.1001/jama.296.1.56

Laviolette, S. R., & van der Kooy, D. (2003). The motivational valence of nicotine in the rat ventral tegmental area is switched from rewarding to aversive following blockade of the $\alpha 7$ -subunit-containing nicotinic acetylcholine receptor. *Psychopharmacology*, 166, 306–313. doi:10.1007/s00213-002-1317-6

McColl, S. L., Burstein, A. H., Reeves, K. R., Billing, C. B., Jr., Stolar, M., & Sellers, E. M. (2008). Human abuse liability of the smoking cessation drug varenicline in smokers and non-smokers. *Clinical Pharmacology & Therapeutics*, 83, 607–614. doi:10.1038/sj.clpt.6100510

Mihalak, K. B., Carroll, F. I., & Luetje, C. W. (2006). Varenicline is a partial agonist at $\alpha 4\beta 2$ and a full agonist at $\alpha 7$ neuronal nicotinic receptors. *Molecular Pharmacology*, 70, 801–805. doi:10.1124/mol.106.025130

Palmatier, M. I., Evans-Martin, F. F., Hoffman, A., Caggiula, A. R., Chaudhri, N., Donny, E. C., et al. (2006). Dissociating the primary reinforcing and reinforcement-enhancing effects of nicotine using a rat self-administration paradigm with concurrently available drug and environmental reinforcers. *Psychopharmacology*, 184, 391–400. doi:10.1007/s00213-005-0183-4

Palmatier, M. I., Matteson, G. L., Black, J. J., Liu, X., Caggiula, A. R., Craven, L., et al. (2007). The reinforcement enhancing effects of nicotine depend on the incentive value of non-drug reinforcers and increase with repeated drug injections. *Drug and Alcohol Dependence*, 89, 52–59. doi:10.1016/j.drugalcdep.2006.11.020

Paterson, N. E., Min, W., Hackett, A., Lowe, D., Hanania, T., Caldarone, B., et al. (2010). The high-affinity nAChR partial

agonists varenicline and sazetidine-A exhibit reinforcing properties in rats. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 34, 1455–1484. doi:10.1016/j.pnpbp.2010.07.037

Picciotto, M. R. (2003). Nicotine as a modulator of behavior: Beyond the inverted U. *Trends in Pharmacological Science*, 23, 494–499. doi:10.1016/S0165-6147(03)00230-X

Quick, M. W., & Lester, R. A. (2002). Desensitization of neuronal nicotinic receptors. *Journal of Neurobiology*, 53, 457–478. doi:10.1002/neu.10109

Rollema, H., Chambers, L. K., Coe, J. W., Glowa, J., Hurst, R. S., Lebel, L. A., et al. (2007). Pharmacological profile of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. *Neuropharmacology*, 52, 985–994. doi:10.1016/j.neuropharm.2006.10.016

Rollema, H., Coe, J. W., Chambers, L. K., Hurst, R. S., Stahl, S. M., & Williams, K. E. (2007). Rationale, pharmacology and clinical efficacy of partial agonists of $\alpha 4\beta 2$ nACh receptors for smoking cessation. *Trends in Pharmacological Science*, 28, 316–325. doi:10.1016/j.tips.2007.05.003

Spiller, K., Xi, Z. X., Li, X., Ashby, C. R., Callahan, P. M., Tehim, A., et al. (2009). Varenicline attenuates nicotine-enhanced brain-stimulation reward by activation of $\alpha 4\beta 2$ nicotinic receptors in rats. *Neuropharmacology*, 57, 60–66. doi:10.1016/j.neuropharm.2009.04.006

Stafford, D., LeSage, M. G., & Glowa, J. R. (1998). Progressive-ratio schedules of drug delivery in the analysis of drug self-administration: A review. *Psychopharmacology*, 139, 169–184. doi:10.1007/s002130050702

Stead, L. F., Perera, R., Bullen, C., Mant, D., & Lancaster, T. (2008). Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Review*, (23), CD000146.