BRIEF REPORT

Possible Reinforcement Enhancing Effects of Bupropion During Initial Smoking Abstinence

Kenneth A. Perkins PhD, Joshua L. Karelitz MA, Nancy C. Jao BS, Erin Stratton BA

Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA

Corresponding Author: Kenneth A. Perkins, Ph.D., Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213, USA. Telephone: (412) 246–5395; Fax: (412) 246–5390; E-mail: perkinska@upmc.edu

Received July 30, 2012; accepted September 7, 2012

ABSTRACT

Introduction: Due to a drop in nicotine, smoking cessation may attenuate reinforcement from sensory stimuli unrelated to nicotine intake. Recent rodent research suggests that bupropion may reverse this attenuation, perhaps helping explain its efficacy in aiding cessation.

Methods: In a within-subjects, crossover study, smokers responded on a simple computer task for brief music reward available on a progressive ratio 50% schedule. Testing was done on three separate occasions: after ad lib smoking during prequit baseline and on the first day of two brief quit attempts while taking bupropion or placebo, in counter-balanced order. Number of operant responses was the measure of reinforcement. To more clearly assess abstinence and medication effects, those meeting 24-hr abstinence criteria ($CO < 5$ ppm; $n = 5$) or clearly failing to abstain ($CO > 10$ ppm; $n = 5$) during both medication conditions were compared.

Results: Among abstainers, repeated measures ANOVA showed that reinforced responding decreased by nearly 50% from baseline after quitting on placebo ($p = .03$), while responding after quitting on bupropion was similar to that during baseline (-17% ; $p = .20$). In contrast, those unable to abstain showed virtually identical reinforced responding due to either medication or baseline.

Conclusions: These exploratory findings confirm that responding for a reward unrelated to smoking decreases after abstinence and are consistent with animal research showing bupropion effects on enhancing reinforced responding.

INTRODUCTION

Aside from nicotine's primary and secondary (e.g. drug cues) reinforcing effects (Caggiula et al., 2001; Corrigall, 1999; Fowler & Kenny, 2011), animal research indicates that nicotine may enhance the reinforcing value of rewards, especially sensory stimuli, that are independent of nicotine intake (Caggiula et al., 2009; Donny et al., 2003; Olausson, Jentsch, & Taylor, 2004; Raiff & Dallery, 2008). Support in humans for this reinforcement enhancing effect of nicotine is suggestive but perhaps specific to reward type, dependence level, measure of reinforcement, or other procedural factors (e.g. Attwood, Penton-Voak, & Munafò, 2009; Barr, Pizzagalli, Culhane, Goff, & Evins, 2008; Dawkins, Powell, West, Powell, & Pickering, 2006; McGrath, Barrett, Stewart, & Schmid, 2012; Perkins, Grottenhaler, & Wilson, 2009).

A key implication of these findings is that quitting smoking would result in removal of these reinforcement enhancing effects of nicotine, decreasing the reinforcing value of rewarding stimuli in an ex-smoker's environment, as indicated in

rodent research (e.g. Weaver et al., 2012). Consistent with this notion, 10-hr smoking abstinence decreased performance on a card-sorting task reinforced by money (Powell, Dawkins, & Davis, 2002) as well as self-reported pleasure in response to movie clips (Dawkins, Acaster, & Powell, 2007). Resumption of nicotine intake by smoking presumably would restore the reinforcing value of these stimuli, perhaps helping to explain why smoking lapses so often result in relapse (e.g. Shadel et al., 2011).

Another critical implication of this research is that cessation medications may aid quitting by attenuating this decline in reinforcement from environmental stimuli due to the loss of nicotine intake. Intriguingly, responding for a rewarding visual stimulus is enhanced by bupropion in a manner similar to that of nicotine (e.g. Palmatier et al., 2009), consistent with other preclinical research on bupropion (Paterson, Balfour, & Markou, 2008). We know of no prior research in humans examining the effects of cessation medications, including bupropion, on enhancement of reinforced responding, although nicotine lozenge may enhance card-sorting performance after

doi:10.1093/ntr/nts224

Advance Access publication October 24, 2012

© The Author 2012. Published by Oxford University Press on behalf of the Society for Research on Nicotine and Tobacco. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

Bupropion and reinforcement enhancement

overnight abstinence in heavier (>15/day) but not lighter smokers (Dawkins et al., 2006).

This exploratory within-subjects study assessed reinforced responding after 24-hr abstinence, while using bupropion during 1 week-long “practice” quit attempt and while using placebo during another quit attempt (counter-balanced). Responding on a simple operant computer task was reinforced by 30-s clips of subjects’ preferred music, which we selected as the “sensory” reinforcer to test because animal research shows that nicotine’s reinforcement enhancing effects may be specific to sensory (e.g. visual stimuli) but not nonsensory (e.g. food) rewards (Caggiula et al., 2009; Raiff & Dallery, 2008). We also related reinforced responding to craving and withdrawal to examine potential associations with symptoms of abstinence (e.g. Dawkins et al., 2007; Powell et al., 2002).

METHODS

Participants

Participants were 10 healthy adult dependent smokers recruited for a study testing ability to quit for at least 24hr during two short-term periods while on bupropion or on placebo medication in a crossover design, similar to that described elsewhere (Perkins et al., 2010). All were recruited partly based on their high interest in making a permanent quit attempt upon completion of the study, defined as wanting to quit within 3 months. All met DSM-IV nicotine dependence criteria (adapted from Breslau, Kilbey, & Andreski, 1994), smoked >10 cigarettes/day for >1 year, and provided a screening expired-air carbon monoxide (CO) of at least 10 ppm. They also completed the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991).

As described in Procedures section, below, only subjects able to meet 24-hr abstinence criteria during the first day of both quit attempts, on bupropion and on placebo ($n = 5$), were assessed for medication effects on reinforced responding during abstinence. Of those able to quit (three men and two women), four were Caucasian and one of unknown ethnicity, and mean (standard deviation [SD]) characteristics were 24.6 (3.6) years old, 15.2 (4.8) cigarettes/day, and 4.2 (1.3) FTND score. For comparison, we also examined responding in those unable to quit during the first day of both medication conditions ($n = 5$). Of those unable to quit (five women), three were Caucasian and two Blacks, and mean characteristics were 39.0 (5.6) years old, 14.8 (4.6) cigarettes/day, and 6.0 (1.6) FTND score.

Reinforcement Task

Reinforcement was determined by number of responses on a modified operant computer program called “Applepicker” (AP; Norman & Jongerius 1985), used in many prior studies (e.g. Epstein, Bulik, Perkins, Caggiula, & Rodefer, 1991; Perkins, Epstein, Grobe, & Fonte, 1994). The available reinforcer was 30 s of the participant’s preferred music, provided by the participant in an electronic format (e.g. CD) during screening. The AP task required using arrows on a keypad to move a cursor around a “field” of “trees” on a monitor, looking for “apples.” Pressing a button on the keypad constituted a response, and finding an apple signaled that 30 s of music (i.e. one reinforcer) had been earned. The number of responses required to find an

apple was on a progressive ratio (PR) schedule, incrementing by 50% (i.e. PR50%), starting with 10 responses for the first reinforcer. When a reinforcer was earned, an apple symbol briefly appeared as feedback, and the music played immediately for 30 s. Upon earning a reinforcer, subjects could continue responding on the AP task without interruption, to extend the time of music. They were free to stop responding at any point and read available magazines while waiting for the end of the 15-min task period (see Perkins et al., 2009).

Procedures

Ability to abstain from smoking for 24hr, defined as 0 cigarettes and confirmed by CO < 5 ppm (Javors, Hatch, & Lamb, 2005), was a dependent measure in the primary study, which assessed days quit during week-long use of bupropion versus placebo, administered double-blind (see similar procedures in Perkins et al., 2010). Testing occurred on three occasions: after smoking *ad libitum* during the baseline week prior to receiving any medication, and on the first day of each of 2 week-long quit attempts on bupropion or on placebo, with the order of medication conditions counter-balanced. Each quit attempt was preceded by a week of dose run up. Upon arrival to each session, participants provided expired-air CO and completed the Questionnaire on Smoking Urges-brief measure of craving (Cox, Tiffany, & Christen, 2001) and the Minnesota Nicotine Withdrawal Scale measure of withdrawal (Hughes & Hatsukami, 2007). They then engaged in the AP task for music reinforcement in a quiet room with no one else present. During the prequit baseline, all subjects *ad lib* smoked in the lab immediately prior to the AP task to equate time since last cigarette. These three AP task sessions were separated by at least 10 days, with all participants resuming smoking (if quit) after each medication condition.

To assess effects of bupropion and placebo on reinforced responding during smoking abstinence, only those who were able to quit during both medication conditions were examined. For comparison, we also assessed any effects of these medications on responding among those who were unable to abstain during both medication conditions, defined as CO > 10 ppm. (12 others had partial abstinence during one or both conditions.) The number of cigarettes smoked in the prior 24hr was assessed at prequit baseline and during the medication conditions via self-monitoring form. Participants were paid for participation, in addition to being offered free counseling and bupropion to make a permanent quit smoking attempt after the end of the larger study. This research was approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent for participation after the nature and consequences of the study was explained.

Analyses

A repeated measures analysis of variance (ANOVA) compared reinforced responding during the prequit baseline with responding while on both medication conditions for those who did, and for those who did not, quit during both quit attempts. Follow-up ANOVAs were done separately for each group. Paired comparisons were conducted via LSD *t* tests (Huitema, 1980) to separately determine if responding due to each medication condition differed from baseline. Reinforced responding

was compared with craving and withdrawal at the same session via Pearson correlation.

RESULTS

Mean (*SD*) cigarettes smoked over the prior 24 hr for “quitters” versus “nonquitters,” respectively, were 15.4 ± 6.6 versus 15.8 ± 5.3 at prequit baseline, 0 versus 10.0 ± 4.9 during placebo, and 0 versus 10.4 ± 6.5 during bupropion. Corresponding CO values were 19.4 ± 5.2 versus 30.6 ± 12.2 ppm at prequit baseline, 2.6 ± 1.5 versus 20.6 ± 6.1 ppm during placebo, and 3.0 ± 0.7 versus 23.8 ± 10.5 ppm during bupropion. Thus, “quitters” clearly abstained from smoking for 24 hr at testing during the medication conditions and “nonquitters” did not, although

the latter may have modestly reduced their smoking. Mean (*SE*) craving and withdrawal for these groups are presented by session for illustrative purposes in Figure 1.

The overall repeated measures analysis of variance (ANOVA) on reinforced responding showed a significant interaction of condition by quit status, $F(2,16) = 4.34$, $p < .05$, but no main effect of quit status, $F(1,8) < 1$. For those who quit, results of ANOVA, $F(2,8) = 5.79$, $p < .05$, showed a significant difference in reinforced responding between the prequit smoking baseline and postquit medication conditions (see Figure 2). In pairwise comparisons, mean (*SE*) responding decreased significantly by nearly 50%, dropping by 528 ± 162 responses from baseline to quitting on placebo ($t = 3.27$, $p = .03$), while responding after quitting on bupropion was similar to that during baseline, declining by just 17%, or 179 ± 118 responses ($t = 1.52$, $p = .20$).

Figure 1. Mean (*SE*) craving and withdrawal at initial smoking baseline (BL) and after dose run up on placebo (Plac) and on bupropion (Bup) in those able to quit ($n = 5$) and those unable to quit ($n = 5$) during both medication conditions. Results are shown for illustrative purposes only.

Figure 2. Mean (*SE*) reinforced responding for music reward at the smoking baseline and while using placebo or bupropion during abstinence (“Quit”). Also shown are responses at each testing session among those unable to abstain during both medication conditions (“Not Quit”).

Bupropion and reinforcement enhancement

Although responding during abstinence tended to be greater, by 349 ± 186 responses, for bupropion versus placebo, these medication conditions did not differ significantly ($t = 1.87, p = .13$). In contrast, those unable to quit during both medication conditions showed virtually identical reinforced responding due to either medication versus baseline, $F(2,8) < 1$ (Figure 2).

Finally, the number of reinforced responses was not significantly correlated with either craving ($r = .16, p = .56$) or withdrawal ($r = -.23, p = .41$) in all participants, with no differences in these correlations due to quit status.

DISCUSSION

Our results suggest that reinforced responding decreases after abstinence from smoking when using placebo but is not significantly decreased when using bupropion. Responding in the nonquitters was completely unchanged across the baseline, placebo, and bupropion conditions, perhaps as would be expected given their continuous nicotine exposure via smoking in all three sessions. However, in the quitters, paired comparisons did not show significantly greater reinforced responding during abstinence due to bupropion versus placebo, and so we cannot conclude that bupropion has an absolute reinforcement enhancing effect during cessation.

These results may be limited by the small sample of smokers able to quit with both medication conditions. It is also possible that the nonquitters (all women) differed from the quitters in unknown ways, despite similar smoking rates both overall and just prior to performing the task at baseline. Thus, replication with a larger sample of smokers is clearly needed to warrant any firm conclusions about these effects of smoking cessation and bupropion. In addition, our results may differ with other types of sensory rewards, including those higher in reinforcer strength than the music reward used here (see Palmatier, O'Brien, & Hall, 2012).

Nevertheless, our findings are similar to rodent research showing nicotine withdrawal effects in reducing (Weaver et al., 2012), and bupropion effects (Palmatier et al., 2009) on enhancing, reinforced responding, suggesting some consistency across species (e.g. O'Dell & Khroyan, 2009). Lack of association between reinforced responding and craving or withdrawal is also consistent with clinical research showing that similar decreases in responding or self-reported pleasure due to abstinence are independent of craving or withdrawal (Dawkins et al., 2007; Powell et al., 2002).

Aside from replication of these results, further research should examine the mechanisms of nicotine's actions on reinforced responding, as well as the actions of acute abstinence. For example, nicotine lowers intracranial self-stimulation (ICSS) threshold, indicating increased reward sensitivity (Kenny & Markou, 2006), and cessation of nicotine may do the opposite (increase ICSS threshold), under certain conditions, coinciding with somatic signs of withdrawal (Paterson et al. 2008). However, the fact that we saw no significant correlation of withdrawal severity with reinforced responding suggests the effects of nicotine cessation on reward sensitivity may not be closely tied to withdrawal per se. Further research also should explore bupropion's possible effects on reinforced responding, such as actions at alpha-adrenergic receptors (Palmatier et al., 2009).

In summary, these exploratory findings suggest quitting smoking may not only remove the primary and secondary reinforcing effects of nicotine, but also these reinforcement enhancing effects of nicotine. These effects would decrease overall reinforcement from other rewards in the smoker's environment, especially those sensory in nature. Consequently, a lapse could restore overall reinforcement from rewarding activities, perhaps in a manner similar to the attenuated decline observed with bupropion (Figure 2). Our findings suggest other cessation medications may also prevent loss of reinforced responding after quitting, especially varenicline (Levin et al., 2012), perhaps helping explain their efficacy in maintaining abstinence.

FUNDING

This research was supported by National Institutes of Health Grants CA143187 and DA031218.

DECLARATION OF INTERESTS

Dr. KAP has consulted with Embera Neurotherapeutics on the development of smoking cessation medications unrelated to this article. No other authors have any disclosures.

ACKNOWLEDGMENTS

The authors thank Carolyn Fonte, Jacqueline Sun, and Tiona Jones for their helpful assistance during sessions.

REFERENCES

- Attwood, A. S., Penton-Voak, I. S., & Munafo, M. R. (2009). Effects of acute nicotine administration on ratings of attractiveness of facial cues. *Nicotine & Tobacco Research, 11*, 44–48. doi:10.1093/ntr/ntn006
- Barr, R. S., Pizzagalli, D. A., Culhane, M. A., Goff, D. C., & Evins, A. E. (2008). A single dose of nicotine enhances reward responsiveness in nonsmokers: Implications for development of dependence. *Biological Psychiatry, 63*, 1061–1065. doi:10.1016/j.biopsych.2007.09.015
- Breslau, N., Kilbey, M. M., & Andreski, P. (1994) DSM-IIIIR nicotine dependence in young adults: Prevalence, correlates and associated psychiatric disorders. *Addiction, 89*, 743–754. doi:10.1111/j.1360-0443.1994.tb00960.x
- Caggiula, A. R., Donny, E. C., Palmatier, M., Liu, X., Chaudhri, N., & Sved, A. (2009). The role of nicotine in smoking: A dual-reinforcement model. In R. A. Bevins, & A. R. Caggiula (eds), *The motivational impact of nicotine and its role in tobacco use, Nebraska Symposium on Motivation*, vol. 55 (pp. 91–109). New York, NY: Springer-Verlag.
- Caggiula, A. R., Donny, E. C., White, A. R., Chaudhri, N., Booth, S., Gharib, M. A., . . . Sved, A. F. (2001). Cue dependency of nicotine self-administration and smoking. *Pharmacology, Biochemistry, & Behavior, 70*, 515–530. doi:10.1016/S0091-3057(01)00676-1
- Corrigall, W. A. (1999) Nicotine self-administration in animals as a dependence model. *Nicotine & Tobacco Research, 1*, 11–20.
- Cox, L. S., Tiffany, S. T., & Christen, A. G. (2001). Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine & Tobacco Research, 3*, 7–16. doi:10.1080/14622200020032051

- Dawkins, L., Acaster, S., & Powell, J. H. (2007). The effects of smoking and abstinence on experience of happiness and sadness in response to positively valenced, negatively valenced, and neutral film clips. *Addictive Behaviors*, 32, 425–431. doi:10.1016/j.addbeh.2006.05.010
- Dawkins, L., Powell, J. H., West, R., Powell, J., & Pickering, A. (2006). A double-blind placebo controlled experimental study of nicotine: I—effects on incentive motivation. *Psychopharmacology*, 189, 355–367. doi:10.1007/s00213-006-0588-8
- Donny, E. C., Chaudhri, N., Caggiula, A. C., Evans-Martin, F. F., Booth, S., Gharib, M. A., . . . Sved, A. F. (2003). Operant responding for a visual reinforcer in rats is enhanced by non-contingent nicotine: Implications for nicotine self-administration and reinforcement. *Psychopharmacology*, 169, 68–76. doi:10.1007/s00213-003-1473-3
- Epstein, L. H., Bulik, C. M., Perkins, K. A., Caggiula, A. C., & Rodefer, J. (1991). Behavioral economic analysis of smoking: Money and food as alternatives. *Pharmacology, Biochemistry, & Behavior*, 38, 715–721. doi:10.1016/0091-3057(91)90232-Q
- Fowler, C. D., & Kenny, P. J. (2011). Intravenous nicotine self-administration and cue-induced reinstatement in mice: Effects of nicotine dose, rate of drug infusion, and prior instrumental training. *Neuropharmacology*, 61, 687–698. doi:10.1016/j.neuropharm.2011.05.012
- Heather, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K.-O. (1991). The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction*, 86, 1119–1127. ISSN: 09520481.
- Hughes, J. R., & Hatsukami, D. K. (2007). Instructions for use of the Minnesota Withdrawal Scale-Revised. Retrieved from <http://www.uvm.edu/~hbpl>
- Huitema, B. (1980). *Analysis of covariance and alternatives*. New York, NY: John Wiley & Sons.
- Javors, M. A., Hatch, J. P., & Lamb, R. J. (2005). Cut-off levels for breath carbon monoxide as a marker for cigarette smoking. *Addiction*, 100, 159–167. doi:10.1111/j.1360-0443
- Kenny, P. J., & Markou, A. (2006). Nicotine self-administration acutely activates brain reward systems and induces a long-lasting increase in reward sensitivity. *Neuropsychopharmacology*, 31, 1203–1211. doi:10.1038/sj.npp.1300905
- Levin, M. E., Weaver, M. T., Palmatier, M. I., Caggiula, A. R., Sved, A. F., & Donny, E. C. (2012). Varenicline dose dependently enhances responding for nonpharmacological reinforcers and attenuates the reinforcement-enhancing effects of nicotine. *Nicotine & Tobacco Research*, 14, 299–305. doi:10.1093/ntr/ntr213
- McGrath, D. S., Barrett, S. P., Stewart, S. H., & Schmid, E. A. (2012). The effects of acute doses of nicotine on video lottery terminal gambling in daily smokers. *Psychopharmacology*, 220, 155–161. doi:10.1007/s00213-011-2465-3
- Norman, W. D., & Jongerius, J. L. (1985). Apple Picker: Computer software for studying human responding on concurrent and multiple schedules. *Behavior Research Methods, Instruments, & Computers*, 17, 222–225.
- O'Dell, L. E., & Khroyan, T. V. (2009). Rodent models of nicotine reward: What do they tell us about tobacco abuse in humans? *Pharmacology, Biochemistry, & Behavior*, 91, 481–488. doi:10.1016/j.pbb.2008.12.011
- Olausson, P., Jentsch, J. D., & Taylor, J. R. (2004). Nicotine enhances responding with conditioned reinforcement. *Psychopharmacology*, 171, 173–178. doi:10.1007/s00213-003-1575-y
- Palmatier, M. I., Levin, M. E., Mays, K. L., Donny, E. C., Caggiula, A. R., & Sved, A. F. (2009). Bupropion and nicotine enhance responding for nondrug reinforcers via dissociable pharmacological mechanisms. *Psychopharmacology*, 207, 381–390. doi:10.1007/s00213-009-1666-5
- Palmatier, M. I., O'Brien, L. C., & Hall, M. J. (2012). The role of conditioning history and reinforcer strength in the reinforcement enhancing effects of nicotine in rats. *Psychopharmacology*, 219, 1119–1131. doi:10.1007/s00213-011-2439-5
- Paterson, N. E., Balfour, D. J. K., & Markou, A. (2008). Chronic bupropion differentially alters the reinforcing, reward-enhancing and conditioned motivational properties of nicotine in rats. *Nicotine & Tobacco Research*, 10, 995–1008. doi:10.1080/14622200802097571
- Perkins, K. A., Epstein, L. H., Grobe, J. E., & Fonte, C. (1994). Tobacco abstinence, smoking cues, and the reinforcing value of smoking. *Pharmacology, Biochemistry, & Behavior*, 47, 107–112. doi:10.1016/0091-3057(94)90118-X
- Perkins, K. A., Grotenthaler, A., & Wilson, A. S. (2009). Lack of reinforcement-enhancing effects of nicotine in non-dependent smokers. *Psychopharmacology*, 205, 635–645. doi:10.1007/s00213-009-1574-8
- Perkins, K. A., Lerman, C., Fonte, C., Mercincavage, M., Stitzer, M. L., . . . & Jain, A. (2010). Cross-validation of a new procedure for early screening of smoking cessation medications in humans. *Clinical Pharmacology and Therapeutics*, 88, 109–114. doi:10.1038/clpt.2010.65
- Powell, J., Dawkins, L., & Davis, R. E. (2002). Smoking, reward responsiveness, and response inhibition: Tests of an incentive motivational model. *Biological Psychiatry*, 51, 151–163. doi:10.1016/S0006-3223(01)01208-2
- Raiff, B. R., & Dallery, J. (2008). The generality of nicotine as a reinforcer enhancer in rats: Effects on responding maintained by primary and conditioned reinforcers and resistance to extinction. *Psychopharmacology*, 201, 305–314. doi:10.1007/s00213-008-1282-9
- Shadel, W. G., Martino, S. C., Setodji, C., Cervone, D., Witkiewitz, K., Beckjord, E. G., . . . & Shih, R. (2011). Lapse-induced surges in craving influence relapse in adult smokers: An experimental investigation. *Health Psychology*, 30, 588–596. doi:10.1037/a0023445.
- Weaver, M. T., Sweitzer, M., Coddington, S., Sheppard, J., Verdecchia, N., Caggiula, A. R., . . . Donny, E. C. (2012). Precipitated withdrawal from nicotine reduces reinforcing effects of a visual stimulus for rats. *Nicotine & Tobacco Research*, 14, 824–832. doi:10.1093/ntr/ntr293.