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Comparison of Expired Carbon Monoxide and Plasma Cotinine as Markers of Cigarette Abstinence

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Abstract

The clinical pharmacology of biochemical measures of nicotine exposure has been thoroughly reviewed with regard to usefulness and limitations in detecting abstinence from cigarette smoking. While plasma nicotine concentration measures only acute nicotine exposure, plasma, salivary, and urine cotinine concentrations reflect exposure over an extended period of time. Although, expired carbon monoxide (CO) is frequently used to confirm self reports, it has a relatively short half life, calling into question whether this measure might provide misleading information by exaggerating smoking cessation success rates. To examine this question, we analyzed expired CO, plasma cotinine and self report data collected in a clinical trial in which subjects (N = 207) were randomly assigned to gain- or loss-framed messages for smoking cessation in combination with open label sustained-release bupropion (300mg/day). In examining measurements collected at 6 weeks, 3 and 6 months, results showed that CO significantly overestimated abstinence rates as compared with cotinine, although the discrepancy was less at the later time points. These data suggest that while expired CO is a useful and well established marker in certain contexts, when testing extended abstinence from smoking with non-nicotine medications, cotinine measurements should be preferred.

Keywords

Carbon monoxide (CO); plasma cotinine; self report; smoking; tobacco; abstinence

1. Introduction

The clinical pharmacology of the several biochemical measures of nicotine exposure, including their usefulness and limitations as markers of abstinence, has been thoroughly reviewed (SRNT Subcommittee on Biochemical Verification, 2002). Plasma nicotine concentration is a measure

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only of acute nicotine exposure (or abstinence) consequent to its very rapid disposition (short half life). On the other hand, plasma, salivary and urine cotinine concentrations provide an approximation of average nicotine exposure over a more extended period of time (SRNT Subcommittee on Biochemical Verification, 2002). Expired carbon monoxide (CO) is a well characterized marker of cigarette smoking, but with its short half life, CO only indicates relatively recent exposure (about 6–9 hours) or documents acute abstinence. In contrast, cotinine, by virtue of its longer half life, offers a window of 5–7 days for detection of nicotine exposure. Despite this limitation, because it is non-invasive, inexpensive and provides information in real time, expired CO measurements are understandably attractive and have been used to document abstinence in the majority of large scale smoking cessation clinical trials with both nicotine (e.g., nicotine patch, gum, & lozenge; Hays et al., 1999; Hughes et al., 1999; Jamrozik et al., 1984; O'Malley et al., 2006; Shiffman et al., 2002) and non-nicotine medications (e.g., bupropion & varenicline; Ahluwalia et al., 2002; Hurt et al., 1997; Gonzalez et al., 2006; Jorenby et al., 1997, 2006).

Reliable biochemical markers of nicotine exposure are an important adjunct to self reports for the objective evaluation of new approaches to achieving smoking cessation. In the smoking cessation clinical trials literature, the majority of studies with non-nicotine containing medications or behavioral treatments use CO as the sole method for biochemical verification with a cutoff of 9 or 10pmm (e.g., Williams et al., 2007; Gonzalez et al., 2006; Jorenby et al., 2006; Nakamura et al., 2007; Nides et al., 2006; Oncken et al., 2006; Tonstad et al., 2006; Tsai et al., 2007; Tonstad et al., 2003; Gonzalez et al., 2001; Hays et al., 2001; Hurt et al., 1997; Spring et al., 2004; Aubin, et al., 2004; Dalsgarð, et al., 2004; Tashkin, et al., 2001; Tønnesen, et al., 2003; Cox, et al., 2004). We were concerned that short term, or unsustained abstinence that occurs only hours prior to evaluation might provide misleading information, and exaggerate treatment success rates, if expired CO rather than cotinine measurements are used to verify patient self reports. Even though other investigators have raised this concern (Gariti et al., 2002), it appears that the field is consistently still only using CO as the method of biochemical verification, even for newer non-nicotine medications (e.g., varenicline, Gonzalez et al., 2006; Jorenby et al., 2006), and few, if any, clinical trials have systematically compared breath CO to plasma cotinine as measures of abstinence. Our investigation was designed to address this issue by using data from a randomized controlled smoking cessation study utilizing bupropion.

2. Method

2.1. Participants and Procedure

We report an analysis of data collected in a prior clinical trial that investigated varying messages to assist smoking cessation with open label sustained-release (SR) bupropion (Toll et al., 2007). All participants received 150 mg of bupropion SR once per day for 3 days, then twice per day for the duration of the 7-week treatment period (1 week pre- and 6 weeks post-quit; Ahluwalia et al., 2002; Hurt et al., 1997). The message framing intervention included framed video and print messages encouraging smoking abstinence (i.e., 2 short videos, print matter, and a water bottle and air freshener with printed slogans on them). For example, a typical gain-framed message was "In addition to the physical benefits of quitting smoking, it can also have a positive impact on one's social life" and a typical loss-framed message was "In addition to the negative physical effects of smoking, it can have a negative impact on one's social life" (see Toll et al., 2007 for additional examples).

Smoking was assessed using Timeline Followback (TLFB) methodology at each weekly appointment utilizing procedures outlined by Sobell and Sobell (1992, 2003). Specifically, participants were asked to indicate the number of cigarettes they consumed each day at baseline (for the 30 days prior to the screening session) and at all weekly or bi-weekly appointments

(for the preceding weeks; Brandon et al., 1995; Brown et al., 1998). As the message framing intervention was provided via video and print messages, the research assistant that administered the TLFB did not provide the framed messages.

Assays were performed during clinic visits at 6 weeks, and 3 and 6 months after the targeted quit date. Self reported abstinence from smoking was verified at each clinic visit using an exhaled CO level less than or equal to 10 ppm (Toll et al., 2007). Although a cut off of 10 ppm is commonly used in clinical trials, we also reanalyzed the data using cutoffs values of 8, 6 and 4 ppm.

At week 6 (i.e., end of treatment), 3-month follow-up, and 6-month follow-up appointments, blood samples were also obtained and used for determining plasma cotinine concentrations utilizing a modified HPLC procedure (Hariharan et al., 1988). A concentration of less than 25 ng/mL was considered to be in accordance with abstinence. Lack of interferences from bupropion and/or its several serum metabolites was verified by the absence of any peaks that co-eluted with cotinine or the internal standard in patients on bupropion who were abstinent (cotinine free). There were slightly fewer plasma cotinine samples (Week 6 = 13 fewer; 3 Months = 9 fewer; 6 Months = 4 fewer) obtained than CO samples due to the fact that obtaining plasma cotinine requires a blood draw, and it is easier to obtain a breath sample than a blood sample (e.g., sometimes the phlebotomist cannot find a participant's vein). Of those subjects who provided self reports and expired CO measurements, cotinine concentrations were obtained on 92%, 92% and 94% of subjects at six weeks, three and six months respectively.

The average age of participants (N = 207; 48.8% Men; 82.9% White) was 42.2 (*SD* = 11.18), and the mean number of cigarettes smoked per day was 22.7 (*SD* = 9.45). On average, participants reported having smoked for 25.0 years (*SD* = 11.12), and the mean score on the Fagerström Test for Nicotine Dependence (FTND) scale was 5.37 (SD = 2.06). Participants exhibited an average expired CO level of 22.7 ppm (*SD*= 10.06,) and a mean baseline plasma cotinine level of 282.8 ng/mL (*SD*= 126.42) consistent with levels expected for pack a day or greater smokers. This study was approved by the Institutional Review Board (IRB) of the Yale University School of Medicine.

2.2. Data Analysis Plan

We compared self reports of point prevalence (i.e., the preceding 7 days) abstinence with the biochemical markers expired CO and plasma cotinine at the end of the study treatment (6 weeks post-quit) and at the 3- and 6-month follow-ups. We chose to use point prevalence abstinence as our measure of self reported abstinence because this is the most common measure used in smoking cessation clinical trials (Fiore et al., 2000; Hughes et al., 2003). We compared abstinence rates using the following methods: self reports vs. CO, self reports vs. cotinine, CO vs. cotinine, and self report + CO vs. self report + cotinine. Comparisons were presented numerically in tabular format and analyzed statistically using chi-square tests. It should be noted that for the purposes of these analyses, we focused on an "as treated" study sample (i.e., participants that came in to the clinic for appointments) instead of an "intention to treat" sample (i.e., all participants) because we only wanted to compare self-reports, CO and cotinine samples for subjects who actually made reports and provided samples.

3. Results

The results of self report, cotinine, and CO measurements at 6 weeks and 3 and 6 months following the "quit date" are displayed in Tables 1 – 4. As presented in Tables 2 –4, all comparisons were statistically significant at $p = .000$. At 6 weeks, expired CO measurements identified many fewer smokers than either self report or serum cotinine (Table 1). Only 1 (<1%) of the 107 abstainers by self report was identified as a smoker by expired CO testing (cut off

10ppm) while 40 of the 64 (62.5%) admitted smokers were below the threshold for expired CO (Table 2) at 6 weeks. Serum cotinine, on the other hand, identified as smokers 32.3% (32/99) of those abstaining by self report, while 10 out of 59 (16.9%) who reported smoking were not picked up by serum cotinine assay (Table 2). Comparing cotinine with expired CO (Table 3), 60 of the 137 (43.8%) subjects abstinent by CO were identified as smokers by cotinine. Conversely none of those with elevated CO were below the threshold of the cotinine assay. When using CO to verify self reports of abstinence (Table 4), 31 of the 98 reports (31.6%) were not confirmed by the combination of serum cotinine and self report. On the other hand the combination of CO and self report failed to identify any additional smokers amongst those identified as abstainers by both cotinine and self report.

At 3 months, there was greater concurrence between self report and serum cotinine measurements (Tables 1 & 2), with 48 out of 53 (90.6%) self reported abstainers confirmed by cotinine measurements. On the other hand none of the self reported abstainers were above the expired CO threshold, while 21 of the 55 (38.2%) self reported smokers were below the CO threshold (Table 2). A small percentage of admitted smokers (7 out of 50 or 14.0%) were still missed with the cotinine assay. Cotinine measurements were above the smoking threshold for 25% (18 out of 72) of those identified as abstaining by expired CO (Table 3). In contrast to the 6 week timepoint, when using CO to verify self reports of abstinence (Table 4), a much smaller percentage (5 of the 53 reports or 9.4%) was not confirmed by cotinine with self report, whereas the combination of CO and self report again failed to identify any additional smokers amongst those identified as abstainers by both cotinine and self report.

At 6 months, the outcomes derived from self reports and serum cotinine measurements were almost identical (Table 2). Only two of 32 (6.3%) self report abstainers were above the cotinine threshold. The reliability of expired CO was also better at the 6 month time point, confirming 30 of 38 (78.9%) self reported smokers (Table 2), although serum cotinine still identified as smokers 18.2% (8 out of 44) of those below the expired CO threshold (Table 3). When CO was used to verify self reports of abstinence at 6 months (Table 4), only a small percentage (2 of the 32 reports or 6.3%) was not confirmed by cotinine, whereas, again none of those abstaining by both self report and cotinine were contradicted by self report plus CO.

Reanalysis using lower cut offs did show a progressive improvement in ability to identify smokers (Table 1). However, even the lowest cut offs of 4 ppm, and 6 ppm proportionately identified only 63% and 48% as many smokers at 6 weeks as did plasma cotinine (Table 1). In fact, even the lowest cut off of 4ppm identified fewer smokers then did self reports. The additional statistical analyses similarly confirmed the greater efficiency of serum cotinine as compared to lower expired CO cut off's, but are not shown in tables 2–4. At 6 months the results for self reports essentially converged with those for serum cotinine and for the lower expired CO cut offs. However, at 6 months the number of smokers identified using 4ppm slightly exceeded that of both self reports and serum cotinine suggesting a possible loss of specificity at the lowest expired CO cut off.

Since nicotine replacement therapy (NRT) could have confounded the study outcome by increasing the mismatches between cotinine and CO, this was accessed at follow up. There were no users of NRT at six weeks. Three subjects, all of whom showed a mismatch between cotinine (positive) and CO (negative) indicated use of NTR at the three month follow up, two of whom admitted smoking. All three subjects were excluded from the data analysis. One subject who, at six months, indicated use of NTR, and admitted pack a day smoking, was strongly positive by both CO (39 ppm) and cotinine (444 ng/mL). This subject's data was retained since the NTR would not have altered the match between cotinine and CO.

4. Discussion

Considering the short half life of expired CO, its limitations as a marker of extended abstinence is not surprising; although, considering its approximate 2 hour half life, the magnitude of the discrepancy is greater than we expected. Our data indicates that, at least at 6 weeks following the designated quit date, expired CO offered little advantage over self reports as a marker of abstinence by itself. Additionally, it failed to identify a significant proportion of those who admitted continued smoking. However, when used to verify self-reports, which is how CO tests are normally employed in both clinical and research practice, CO fared somewhat better than when it stood alone although 31.6% of abstinence diagnoses were still contradicted by the combination of cotinine plus self report. Serum cotinine assays, on the other hand, highlighted the limitations of self reports of abstinence, although not surprisingly, the reliability of self reports improved over time amongst those who remained in the study. A large proportion of subjects who self-reported abstinence demonstrated cotinine concentrations well above the designated threshold. Thus, for the sample in this study, reliance on expired CO measurements to verify self reports of abstinence might lead to overestimation of treatment efficacy. Of note, the current study is one of the first to compare CO to plasma cotinine. Urine cotinine has also been reported to be more sensitive than expired CO (Gariti et al., 2002) as a measure of abstinence. In a reported comparison with salivary cotinine measurements, expired CO performed more reliably than in the current study, but the sample was different (Murray et al., 1993). That study was concerned with individuals being treated for chronic obstructive pulmonary disease, and the sensitivity and specificity were derived from a “usual treatment” sample of subjects not receiving specific therapy for smoking cessation. The focus was on the relative reliability of biomarkers vs self reports and subjects were only tested anually. Thus, the nature and possibly the motivation of that study population significantly differed from ours.

Notably, the correspondence between measures of abstinence based on CO and those based on cotinine improved during the follow-up period compared to the treatment period. Several factors could contribute to this finding. At the end of treatment, those who smoked may not have returned to regular patterns of smoking whereas at follow-up regular smoking may have been reestablished. Similarly, during treatment, smokers may have been reluctant to admit occasional lapses in smoking abstinence, whereas during follow-up return to smoking may have been easier to acknowledge, particularly if smoking was now more regular. Finally, fewer participants returned at follow-up and perhaps this group was better motivated and more forthright in their reports. While the drop out rate reduced the number of subjects and samples available for analysis at the later times, this limitation reflects common experience with smoking cessation clinical trials. The increasing concurrence between self report, plasma cotinine and CO at the later time points suggests that, at least for some studies, self reports may be sufficient during the long term follow up phase.

It should be noted that when studying nicotine replacement medications such as the transdermal nicotine patch, cotinine cannot be used as a marker of cigarette abstinence, as cotinine is a metabolite of nicotine. Thus, cotinine’s primary use for verification of self reports of abstinence during treatment is limited to non-nicotine containing medications (e.g., bupropion, nortriptyline; Ahluwalia et al., 2002; Hall et al., 2002). However, with varenicline’s recent introduction as a novel and effective smoking cessation agent (Gonzalez et al, 2006; Jorenby et al., 2006), it is likely that there will be several new investigations involving this medication for which measurement of cotinine as a verification of abstinence might be preferable to expired CO.

The time window for detecting smoking is much longer for cotinine than expired CO, but it is still constrained by the rate of cotinine disposition (SRNT Subcommittee on Biochemical Verification, 2002). Cotinine measurements failed to detect a small percentage of admitted

smokers. Presumably, based on the variable half life of cotinine, these subjects had ceased smoking within 2–5 days of the sampling date. We felt that 25 ng/mL was a reliable lower limit of quantitation for our assay. Had we used 15 ng/mL, as has been recommended (SRNT Subcommittee on Biochemical Verification, 2002), it is possible this small discrepancy would have been reduced. However, pack a day smokers can be expected to have serum cotinine levels over 200 ng/mL. The great majority of our positive cotinines were over 199 ng/mL and only 14 (2.6%) of the 546 samples that were cotinine positive were in the 25–49 ng/mL range. Thus, it seems unlikely that those who admitted smoking were using only one to two cigarettes per day. More likely, a few subjects may have had cotinine half lives at the shorter end of the spectrum, and/or the last cigarettes were smoked within a week of the testing day, but more than 3–5 days prior to testing. A lower detection limit of 15 ng/mL would have lengthened the window, and allowed yet more sensitive detection of nicotine exposure, but would not have significantly altered the outcome, and if anything would have reinforced the conclusions of this study. A lower limit may be especially appropriate for a population of lighter smokers than those enrolled in our study. Whether or not our findings can be generalized might be questioned. It is possible that analysis of similarly derived data from clinical trials with alternative study designs and/or different populations might yield different results. However, in our opinion, it is more probable that our findings are intrinsic to the pharmacokinetic properties of the two biochemical markers. Of note, we did not calculate measures of sensitivity and specificity. The limitation to calculating sensitivity and specificity for these data is that there is currently no independent “gold standard” for determining false positives and negatives for the three measures of interest, self report, expired CO and serum cotinine. One could argue that cotinine could be used as the gold standard, but as our data show, using a 1 week interval cotinine misses some smokers; so this would be a compromise.

Our data demonstrate a progressive improvement in the ability of expired CO to identify smokers as the cut off is lowered, but with some apparent modest loss of specificity at 4ppm. However, in the context of this outpatient clinical trial, plasma cotinine retained its considerable superiority to expired CO at all cut off values.

Our results should not be construed as precluding the use of expired CO as a marker of tobacco smoking or as a method to verify abstinence from cigarette smoking. Indeed, its utility for identifying smokers in several contexts, or verifying acute abstinence is well established (e.g., Middleton and Morice, 2000). However, we suggest that with outpatient clinical trials not involving nicotine replacement therapy within the last seven days, wherein confirmation of more extended abstinence is the goal, but testing is relatively infrequent, cotinine measurements should probably be preferred. Even with current nicotine replacement therapy, wherein measurement of non-nicotine derived tobacco markers is required, the limitations of expired CO monitoring still need to be recognized. If phlebotomy is not feasible, non-invasive options such as urine or saliva cotinine measurements should be acceptable, and superior to expired CO.

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References

Acosta MC, Buchhalter AR, Breland AB, Hamilton DCP, Eissenberg T. Urine cotinine as an index of smoking status in smokers during 96-hr abstinence: Comparison between gas chromatography/mass spectrometry and immunoassay test strips. Nicotine Tob Res 2004;6:615–620. [PubMed: 15370157]

Ahluwalia JS, Harris KJ, Catley D, Okuyemi KS, Mayo MS. Sustained-release bupropion for smoking cessation in African Americans: A randomized controlled trial. J Am Med Assoc 2002;288:468–474.

Aubin HJ, Lebargy F, Berlin I, Bidaut-Mazel C, Chemali-Hudry J, Lagrue G. Efficacy of bupropion and predictors of successful outcome in a sample of French smokers: A randomized placebo-controlled trial. Addiction 2004;99:1206–1218. [PubMed: 15317642]

Brandon TH, Copeland AL, Saper ZL. Programmed therapeutic messages as a smoking treatment adjunct: Reducing the impact of negative affect. Health Psychol 1995;14:41–47. [PubMed: 7737072]

Brown RA, Burgess SA, Sales SD, Whiteley JA, Evans DM, Miller IW. Reliability and validity of a smoking Timeline Followback interview. Psychol Addict Behav 1998;12:101–112.

Cox LS, Patten CA, Niaura RS, Decker PA, Rigotti N, Sachs DPL, Buist S, Hurt RD. Efficacy of bupropion for relapse prevention in smokers with and without a past history of major depression. J Gen Intern Med 2004;19:828–834. [PubMed: 15242467]

Dalsgarð ÓJ, Hansen NCG, Søes-Petersen U, Evald T, Høegholm A, Barber J, Vestbo J. A multicenter, randomized, double-blind, placebo-controlled, 6-month trial of bupropion hydrochloride sustained-release tablets as an aid to smoking cessation in hospital employees. Nicotine Tob Res 2004;6:55–61. [PubMed: 14982688]

Fiore, MC.; Bailey, WC.; Cohen, SJ.; Dorfman, SF.; Goldstein, MG.; Gritz, ER.; Heyman, RB.; Jaen, CR.; Kottke, TE.; Lando, HK.; Mecklenburg, RE.; Mullen, PD.; Nett, LM.; Robinson, L.; Stitzer, ML.; Tommasello, AC.; Villejo, L.; Wewers, ME. Treating Tobacco Use and Dependence: Clinical Practice Guideline. U.S. DHHS; Rockville, MD: 2000.

Gariti P, Alterman AI, Ehrman R, Mulvaney FD, O'Brien CP. Detecting smoking following smoking cessation treatment. Drug Alcohol Depend 2002;65:191–196. [PubMed: 11772480]

Gonzales DH, Nides MA, Ferry LH, Kustra RP, Jamerson BD, Segall N, Herrero LA, Krishen A, Sweeney A, Buaron K, Metz A. Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: A randomized placebo-controlled study. Clin Pharmacol Ther 2001;69:438–444. [PubMed: 11406741]

Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR. Varenicline, an alpha-4-beta-2 nicotinic acetylcholine receptor partial agonist, vs. sustained-release bupropion and placebo for smoking cessation: A randomized controlled trial. J Am Med Assoc 2006;296:47–55.

Hall SM, Humfleet GL, Reus VI, Munoz RF, Hartz DT, Maude-Griffin R. Psychological intervention and antidepressant treatment in smoking cessation. Arch Gen Psychiatry 2002;59:930–936. [PubMed: 12365880]

Hariharan M, VanNoord T, Greden JF. A high performance liquid chromatographic method for routine simultaneous determination of nicotine and cotinine in plasma. Clin Chem 1988;34:724–729. [PubMed: 3359608]

Hays JT, Croghan GA, Offord KP, Hurt RD, Schroeder DR, Wolter TD, Nides MA, Davidson M. Over-the-Counter nicotine patch therapy for smoking cessation: Results from randomized, double-blind, placebo-controlled, and open label trials. Am J Public Health 1999;89:1701–1707. [PubMed: 10553392]

Hays JT, Hurt RD, Rigotti NA, Niaura R, Gonzales D, Durcan MJ, Sachs DPL, Wolter TD, Buist AS, Johnston JA, White JD. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation: A randomized, controlled trial. Ann Intern Med 2001;135:423–433. [PubMed: 11560455]

Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: Issues and recommendations. Nicotine Tob Res 2003;5:13–25. [PubMed: 12745503]

Hughes JR, Lesmes GR, Hatsukami DK, Richmond RL, Lichtenstein E, Jorenby DE, Broughton JO, Fortmann SP, Leischow SJ, McKenna JP, Rennard SI, Wadland WC, Heatley SA. Are higher doses

of nicotine replacement more effective for smoking cessation? Nicotine Tob Res 1999;1:169–174. [PubMed: 11072398]

Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, Khayrallah MA, Schroeder DR, Glover PN, Sullivan CR, Croghan IT, Sullivan PM. A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med 1997;337:1195–1202. [PubMed: 9337378]

Jamrozik K, Fowler G, Vessey M, Wald N. Placebo controlled trial of nicotine chewing gum in general practice. Br Med J 1984;289:794–797. [PubMed: 6434084]

Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR. Efficacy of varenicline, an alpha-4-beta-2 nicotinic acetylcholine receptor partial agonist, vs. placebo or sustained-release bupropion for smoking cessation: A randomized controlled trial. J Am Med Assoc 2006;296:56–63.

Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 1999;340:685–691. [PubMed: 10053177]

Middleton ET, Morice AH. Breath carbon monoxide as an indication of smoking habit. Chest 2000;117:758–763. [PubMed: 10713003]

Murray RP, Connett JE, Lauger GG, Voelker HT. Error in smoking measures: effects of intervention on relations of cotinine and carbon monoxide to self-reported smoking. Am J Public Health 1993;83:1251–1257. [PubMed: 8363000]

Nakamura M, Oshima A, Fujimoto Y, Maruyama N, Ishibashi T, Reeves KR. Efficacy and tolerability of varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, in a 12-week, randomized, placebo-controlled, dose-response study with 40-week follow-up for smoking cessation in japanese smokers. Clin Ther 2007;29:1040–1056. [PubMed: 17692720]

Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R, Reeves KR. Smoking cessation with varenicline, a selective α4β2 nicotinic receptor partial agonist: Results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. Arch Intern Med 2006;166:1561–1568. [PubMed: 16908788]

O'Malley SS, Cooney JL, Krishnan-Sarin S, Dubin JA, McKee SA, Cooney NL, Blakeslee A, Meandzija B, Romano-Dahlgard D, Wu R, Makuch R, Jatlow P. Controlled trial of naltrexone augmentation of nicotine replacement for smoking cessation. Arch Intern Med 2006;166:667–674. [PubMed: 16567607]

Oncken C, Gonzales D, Nides M, Rennard S, Watsky E, Billing CB, Anziano R, Reeves K. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. Arch Intern Med 2006;166:1571–1577. [PubMed: 16908789]

Shiffman S, Dresler CM, Hajek P, Gilburt SJA, Targett DA, Strahs KR. Efficacy of a nicotine lozenge for smoking cessation. Arch Intern Med 2002;162:1267–1276. [PubMed: 12038945]

Sobell, LC.; Sobell, MB. Timeline Follow-back: A technique for assessing self-reported alcohol consumption. In: Litten, R.; Allen, J., editors. Measuring Alcohol Consumption. The Humana Press Inc.; Rockville, MD: 1992. p. 207-224.

Sobell, LC.; Sobell, MB. Alcohol consumption measures. In: Allen, JP.; Wilson, VB., editors. Assessing Alcohol Problems: A Guide for Clinicians and Researchers. 2. National Institute on Alcohol Abuse & Alcoholism; Bethesda, MD: 2003. p. 75-99.

Spring B, Doran N, Pagoto S, Schneider K, Pingitore R, Hedeker D. Randomized controlled trial for behavioral smoking and weight control treatment: Effect of concurrent versus sequential intervention. J Consult Clin Psychol 2004;72:785–796. [PubMed: 15482037]

SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. Nicotine Tob Res 2002;4:149–159. [PubMed: 12028847]

Tashkin DP, Kanner R, Bailey W, Buist S, Anderson P, Nides MA, Gonzales D, Dozier G, Patel MK, Jamerson BD. Smoking cessation in patients with chronic obstructive pulmonary disease: A double-blind, placebo-controlled, randomised trial. Lancet 2001;357:1571–1575. [PubMed: 11377644]

Toll BA, O'Malley SS, Katulak NA, Wu R, Dubin JA, Latimer A, Meandzija B, George TP, Jatlow P, Cooney JL, Salovey P. Comparing gain-and loss-framed messages for smoking cessation with

sustained-release bupropion: A randomized controlled trial. Psychol Addict Behav 2007;21:534–544. [PubMed: 18072836]

Tønnesen P, Tonstad S, Hjalmarson A, Lebargy F, Van Spiegel PI, Hider A, Sweet R, Townsend J. A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. J Intern Med 2003;254:184–192. [PubMed: 12859700]

Tonstad S, Farsang C, Klaene G, Lewis K, Manolis A, Perruchoud AP, Silagy C, van Spiegel PI, Astbury C, Hider A, Sweet R. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. Eur Heart J 24:946–955. [PubMed: 12714026]

Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: A randomized controlled trial. J Am Med Assoc 2006;296:64–71.

Tsai S, Cho H, Cheng H, Kim C, Hsueh K, Billing CB Jr, Williams KE. A randomized placebo-controlled trial of varenicline, a selective $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in asian smokers. Clin Ther 2007;29:1027–1039. [PubMed: 17692719]

Williams KE, Reeves KR, Billing CB Jr, Pennington AM, Gong J. A double-blind study evaluating the long-term safety of varenicline for smoking cessation. Curr Med Res Opin 2007;23:793–801. [PubMed: 17407636]

Table 1

Abstinence by Self Report, Cotinine, and CO at Week 6, 3 Months, and 6 Months

	Abstinent	Smoking	Total
Week 6			
Self Report	107 (62.6%)	64 (37.4%)	171
Serum Cotinine	77 (48.7%)	81 (51.3%)	158
Expired CO = 10ppm	146 (85.4%)	25 (14.6%)	171
8ppm	141 (82.5%)	30 (17.5%)	171
6ppm	132 (77.2%)	39 (22.8%)	171
4ppm	116 (67.8%)	55 (32.2%)	171
3 Month			
Self Report	57 (50.9%)	55 (49.1%)	112
Serum Cotinine	55 (53.4%)	48(46.6%)	103
Expired CO = 10ppm	78 (69.6%)	34 (30.4%)	112
8ppm	73 (65.2%)	39 (34.8%)	112
6ppm	68 (60.7%)	44 (39.3%)	112
4ppm	59 (52.7%)	53 (47.3%)	112
6 Month			
Self Report	34 (47.2%)	38 (52.8%)	72
Serum Cotinine	32 (47.1%)	36 (52.9%)	68
Expired CO = 10ppm	42 (58.3%)	30 (41.7%)	72
8ppm	34 (47.2%)	38 (52.8%)	72
6ppm	39 (54.2%)	33 (45.8%)	72
4ppm	31 (43.1%)	41 (56.9%)	72

Table 2

Self Reports of Point Prevalence Abstinence Versus Biochemical Measurements of CO and Cotinine

	Self Report of Point Prevalence Abstinence			χ^2	*p*
	Abstinent	Smoking	Total		
Carbon Monoxide:					
Week 6					
Abstinent	106	40	146	42.90	.000
Smoking	1	24	25		
Total	107	64	171		
3 Month					
Abstinent	57	21	78	50.60	.000
Smoking	0	34	34		
Total	57	55	112		
6 Month					
Abstinent	34	8	42	46.02	.000
Smoking	0	30	30		
Total	34	38	72		
Cotinine:					
Week 6					
Abstinent	67	10	77	38.08	.000
Smoking	32	49	81		
Total	99	59	158		
3 Month					
Abstinent	48	7	55	60.61	.000
Smoking	5	43	48		
Total	53	50	103		
6 Month					
Abstinent	30	2	32	52.89	.000
Smoking	2	34	36		
Total	32	36	68		

Table 3

CO Versus Cotinine

	Cotinine			χ^2	*p*
	Abstinent	Smoking	Total		
Week 6 CO					
Abstinent	77	60	137	22.06	.000
Smoking	0	20	20		
Total	77	80	157		
3 Month CO					
Abstinent	54	18	72	44.86	.000
Smoking	1	30	31		
Total	55	48	103		
6 Month CO					
Abstinent	36	8	44	46.89	.000
Smoking	1	32	33		
Total	37	40	77		

Table 4

Self Report + CO Versus Self Report + Cotinine

	Self Report + Cotinine			χ^2	*p*
	Abstinent	Smoking	Total		
Week 6 Self Report + CO					
Abstinent	67	31	98	70.37	.000
Smoking	0	59	59		
Total	67	90	157		
3 Month Self Report + CO					
Abstinent	48	5	53	84.80	.000
Smoking	0	50	50		
Total	48	55	103		
6 Month Self Report + CO					
Abstinent	30	2	32	60.40	.000
Smoking	0	36	36		
Total	30	38	68		