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## Short Communication

## Promoting smoking abstinence among patients with chronic obstructive pulmonary disease: Initial feasibility

Joanna M. Streck<sup>a</sup>, Taylor A. Ochalek<sup>a</sup>, Mollie E. Miller<sup>b</sup>, Andrew C. Meyer<sup>c</sup>, Gary Badger<sup>d</sup>, Charlotte Teneback<sup>e</sup>, Anne Dixon<sup>e</sup>, Stephen T. Higgins<sup>a,c</sup>, Stacey C. Sigmon<sup>a,c,\*</sup>

<sup>a</sup> University of Vermont (UVM) Department of Psychological Science, United States

<sup>b</sup> Brown University Department of Psychiatry and Human Behavior, United States

<sup>c</sup> UVM Department of Psychiatry, United States

<sup>d</sup> UVM Department of Medical Biostatistics, United States

<sup>e</sup> UVM Department of Medicine, United States

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## ABSTRACT

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the U.S., with the majority of COPD deaths attributable to cigarette smoking. Despite this, individuals with COPD have a higher prevalence of smoking, poorer quit rates, and higher relapse rates compared to smokers without a COPD diagnosis. We examined the feasibility of an incentives-based intervention for producing an initial period of biochemically-verified smoking abstinence among daily smokers with COPD. Participants were randomly assigned to a Contingent (n = 13) or Noncontingent (n = 16) incentives condition and visited the clinic for 14 consecutive days. Contingent participants earned vouchers with monetary value contingent on breath carbon monoxide (CO) levels during Study Days 1–5 and urinary cotinine during Days 6–14. Voucher earnings began at \$9.00 and increased by \$1.50 with each subsequent negative sample for maximum possible of \$362.50. Noncontingent participants received vouchers of comparable value independent of smoking status. Differences between conditions varied across study days for daily smoking abstinence ( $X^2 = 45.27, p < 0.0001$ ), CO (F(13, 280) = 1.95,  $p = 0.025$ ), and cotinine (F(13, 279) = 2.20,  $p = 0.010$ ), with generally higher rates of abstinence and lower CO and cotinine levels observed in the Contingent vs. Noncontingent conditions. Results from this randomized pilot study support the potential efficacy of an incentives-based intervention for reducing cigarette smoking among individuals with COPD. Further research efforts should seek to promote and evaluate longer-term abstinence and associated changes in respiratory function.

## 1. Introduction

Cigarette smoking is the leading cause of preventable death and is responsible for nearly half a million premature deaths annually in the United States. Pulmonary disease is a particularly serious smoking-related health consequence (U.S. Department of Health and Human Services, 2014). Prevalence of smoking among individuals with chronic obstructive pulmonary disease (COPD) far exceeds that of the general population (38–77% vs. 15%, respectively), and an estimated 80% of all COPD deaths are attributable to smoking (U.S. Department of Health and Human Services, 2014; Tønnesen, 2013; Jamal, 2016). Furthermore, rates of COPD-related deaths have dramatically increased over the past twenty-five years, such that they now represent the country's 3rd leading cause of death (USDHHS, 2017).

Smoking cessation is the single most cost-effective intervention to

reduce the risk of developing COPD, slow the rate of disease progression, and dramatically reduce COPD-related mortality (Anthonisen et al., 2005; GOLD, 2017; Wu and Sin, 2011). Despite the importance of quitting smoking in this group, smokers with COPD often present with several characteristics previously associated with poorer cessation outcomes, including greater nicotine dependence severity, smoking more cigarettes per day, higher levels of depression, and lower levels of self-efficacy to quit smoking (Jiménez-Ruiz et al., 2001; van Eerd et al., 2015). Studies have also documented poorer quit rates (Hoogendoorn et al., 2010) and higher relapse rates (Wagena et al., 2005) among smokers with vs. without a COPD diagnosis. Taken together, smokers with COPD may represent a particularly vulnerable and challenging population for whom more intensive cessation interventions are needed. Indeed, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that all smokers at risk for and

\* Corresponding author at: UHC-SATC Room 1415, 1 South Prospect Street, Burlington, VT 05401, United States.  
E-mail address: [stacey.sigmon@uvm.edu](mailto:stacey.sigmon@uvm.edu) (S.C. Sigmon).

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diagnosed with COPD be offered the most intensive smoking-cessation intervention feasible (GOLD, 2017).

Over the past two decades our research group has been developing and evaluating an intensive behavioral intervention for promoting smoking abstinence among individuals at elevated risk for smoking and smoking-related consequences. Contingency management (CM) is a behavioral approach wherein patients earn tangible incentives contingent upon providing objective evidence of behavior change (Higgins et al., 2008). Consistent with an extensive literature demonstrating CM's efficacy in reducing illicit drug use, a large body of evidence also supports its efficacy in reducing cigarette smoking (Sigmon and Patrick, 2012; Davis et al., 2016). This includes studies specifically focused on promoting smoking abstinence among challenging smoker populations, such as individuals with concurrent opioid use disorder and other substance use disorders, individuals with serious mental illness and pregnant smokers (Sigmon and Patrick, 2012; Davis et al., 2016; Higgins et al., 2012). Considering that smoking-related morbidity and mortality among COPD patients continues to rise, our aim in this randomized pilot study was to begin examining whether CM may be effective in promoting smoking abstinence among smokers diagnosed with COPD. More specifically, we sought to test the feasibility of procedures for promoting abstinence in the initial two weeks of the cessation effort, as early abstinence is key to achieving longer-term success.

## 2. Methods

### 2.1. Participants

Participants were recruited through flyers distributed in the community and local pulmonary clinic. Eligible participants were  $\geq 35$  years of age, reported smoking  $\geq 5$  cigarettes per day, and had been diagnosed with COPD (i.e., post-bronchodilator FEV1/FVC ratio  $\leq 0.70$ ), with COPD severity defined using GOLD (2017) staging guidelines. Individuals who provided a urine specimen positive for illicit drugs at intake were excluded, as were those who were pregnant, nursing or had serious or unstable medical disorders that may affect study participation.

### 2.2. Assessments

At intake, participants completed the Fagerström Test for Cigarette Dependence (FTCD), (Fagerström, 2012) a Time Line Follow Back (TLFB) (Sobell and Sobell, 1992) interview assessing past-month use of cigarettes and any other nicotine sources, and a demographic and smoking history questionnaire developed by our research group. They provided urine and breath samples for biochemical verification of recent smoking, alcohol, and drug use. Participants provided consent to confirm COPD diagnosis with their primary care provider and received \$35 for completing the intake screening. A modified version of the intake assessment was administered at the end of the study.

### 2.3. Study design

Eligible participants provided informed consent and received a brief smoking-cessation educational session prior to the study and the National Cancer Institute (2003) booklet, "Clearing the Air: Quit Smoking Today." Staff reviewed its contents with participants and answered any questions. Participants were then randomly assigned to one of two experimental conditions: Contingent ( $n = 13$ ) or Noncontingent ( $n = 16$ ). Stratification variables included gender (male, female), COPD severity (FEV1  $\leq 50\%$ ,  $> 50\%$ ), and interest in smoking pharmacotherapy (yes, no). While no pharmacotherapy was offered as part of the intervention, interest in pharmacotherapy was used as a stratification variable to minimize the chance that pharmacotherapy use would be confounded with treatment assignment should any participants

decide to use a pharmacotherapy during the study. Participants were informed of their group assignment and worked with staff to set a quit date. Beginning on their quit date, they visited the clinic daily for 14 consecutive days. At each visit, participants provided breath carbon monoxide (CO) and urinary cotinine samples and reported any past 24-h use of prescription or over-the-counter medications, smoking or nicotine replacement therapy. Those randomized to the Contingent condition earned monetary vouchers contingent on providing biochemical verification of smoking abstinence, while those in the Noncontingent condition received voucher earnings independent of their smoking status (described below).

### 2.4. Biochemical monitoring

Expired breath CO was assessed using a handheld monitor (Bedfont EC50 Smokerlyzer; Bedfont Scientific Ltd., Kent, UK), and urinary cotinine, a metabolite of nicotine, was analyzed via on-site enzyme multiplied immunoassay (Microgenics, Fremont, CA, USA). On Study Days 1–5, abstinence was defined as CO  $\leq 6$  ppm. On Days 6–14, abstinence was defined as urinary cotinine  $\leq 80$  ng/ml. CO (relatively short half-life) was used instead of cotinine (relatively long half-life) earlier in the intervention to avoid carry-over from smoking prior to the quit date which could interfere with providing reinforcement for early smoking abstinence; the cotinine measure was used later to provide a more sensitive and specific test that can detect even low levels of ongoing smoking (Dunn et al., 2008).

### 2.5. Experimental conditions

Participants randomized to the Contingent condition earned voucher-based incentives for providing breath CO samples  $\leq 6$  ppm during Days 1–5, with the first negative sample worth \$9.00 and subsequent negative samples escalating by \$1.50. To further promote early abstinence, COs  $\leq 4$  ppm earned an additional \$10.00 bonus. To encourage participants to successfully transition from CO to the more stringent cotinine cutoff on Day 6, a bonus of \$50.00 was available for successfully meeting the criterion on that day. A positive or a missing sample resulted in no vouchers for that day and reset the value of the next negative sample to the initial \$9.00, with two consecutive negatives thereafter returning the schedule to the pre-reset value. Participants in the Contingent condition could earn a maximum of \$362.50 in vouchers. Vouchers were redeemable for gift cards from local and online retailers and services.

Noncontingent participants received vouchers independent of smoking status, with their schedule and value of voucher delivery based on average expected earnings in the Contingent condition in order to balance levels of clinic contact, monitoring, and material support across the two experimental groups. To further emphasize that voucher delivery was not linked to smoking status, vouchers were provided prior to collection of biochemical samples.

### 2.6. Data analysis

Participants were compared on demographic and smoking characteristics using chi square tests for categorical variables and *t*-tests for continuous variables. Repeated measures analyses based on generalized estimating equations were used to evaluate group and time effects and their interaction on biochemically-verified abstinence (i.e., percent abstinence across all study days) across the study. Mixed model repeated measure analyses were used to evaluate group and time effects and their interaction on the two biochemical measures (i.e., cotinine and CO) across the 14-day study, which were log transformed prior to analyses. After determining that intervention effects varied across time as evidenced by a significant group by time interaction, chi square tests were used to evaluate group differences on each day of the intervention. Biochemically-verified abstinence was defined as a CO  $\leq 6$  ppm during

**Table 1**  
Participant characteristics<sup>a</sup>.

	All (n = 29)	Contingent (n = 13)	Noncontingent (n = 16)	p-Value
<b>Demographic Characteristics</b>				
Age, years.	57.0 (7.5)	55.8 (6.8)	57.9 (8.1)	0.45
Education, years.	12.8 (2.4)	12.8 (1.8)	12.8 (2.9)	0.98
Male, % (n)	52 (16)	54 (7)	50 (8)	0.84 <sup>b</sup>
<b>Smoking Characteristics</b>				
Number of cigarettes/day	22.8 (20.4)	16.9 (6.3)	27.5 (26.3)	0.14
Age of first cigarette, years.	13.3 (4.1)	13.5 (3.4)	13.3 (4.7)	0.89
Age started smoking regularly, years.	15.7 (4.7)	15.3 (4.4)	16.1 (5.1)	0.66
FTCD <sup>c</sup> total score (0–10)	6.0 (2.2)	5.6 (2.0)	6.3 (2.5)	0.46
Breath CO level, ppm	11.4 (7.0)	10.3 (4.5)	12.2 (8.6)	0.44
Urine cotinine level, ng/ml	1168 (560)	1167 (589)	1169 (555)	0.99
Number of prior quit attempts	16.4 (21.0)	12.5 (7.6)	19.3 (27.0)	0.35
Duration of longest quit, days, median (IQR)	92 (8, 695)	60 (3, 225)	210 (25, 908)	0.21 <sup>d</sup>
<b>Pulmonary Characteristics</b>				
FEV1/FVC	56.5 (12.7)	52.4 (13.3)	59.9 (11.6)	0.12
FEV1 (% normal)	57.7 (21.1)	51.8 (22.3)	62.5 (19.5)	0.18

<sup>a</sup> Values are Mean (SD) with significance based on two sample *t*-tests unless otherwise specified.

<sup>b</sup> Significance based on chi square test.

<sup>c</sup> FTCD, Fagerstrom Test for Cigarette Dependence (Fagerstrom, 2012).

<sup>d</sup> Significance based on Wilcoxon Rank Sum test.

Study Days 1–5 and cotinine  $\leq$  80 ng/ml for Days 6–14. Participants who did not provide biochemical samples were counted positive for smoking at that time point consistent with an intent-to-treat approach. Retention was examined by computing the percentage of participants in each group who completed the study using a chi square analysis. All analyses were performed using SAS statistical software (SAS Institute, Cary, NC) with significance based on  $\alpha = 0.05$ .

### 3. Results

On average, participants were 57 years old and had completed 13 years of education (Table 1). They smoked 23 cigarettes per day, had smoked regularly for over 40 years and reported an average of 16 prior quit attempts. In terms of pulmonary health, participants presented with mean FEV1/FVC and FEV1 (% normal) values of 0.57 and 58% predicted, respectively, indicating moderately severe COPD, with 38% of participants meeting clinical criteria for severe or very severe COPD. Contingent and Noncontingent participants did not differ on any demographic, smoking, or pulmonary characteristics at study intake. Additionally, 85% and 88% of Contingent and Noncontingent participants, respectively, completed the 14-day study ( $\chi^2 = 0.05$ ,  $p = 0.82$ ).

When smoking abstinence across study visits was examined (defined as CO  $\leq$  6 ppm on Days 1–5 and cotinine  $\leq$  80 ng/ml on Days 6–14), differences in abstinence between groups varied across study days ( $\chi^2 = 45.27$ ,  $p < 0.0001$ ). While both groups presented with generally similar levels of CO-defined abstinence during Days 1–5, differences between groups became pronounced following the transition to the more stringent cotinine-based abstinence during Days 6–14. Contingent participants provided a significantly greater percent of smoking-abstinent samples than Noncontingent participants on Study Days 9, 10, 11, 13 and 14 ( $p$ 's  $< 0.05$ ; Fig. 1, upper panel).

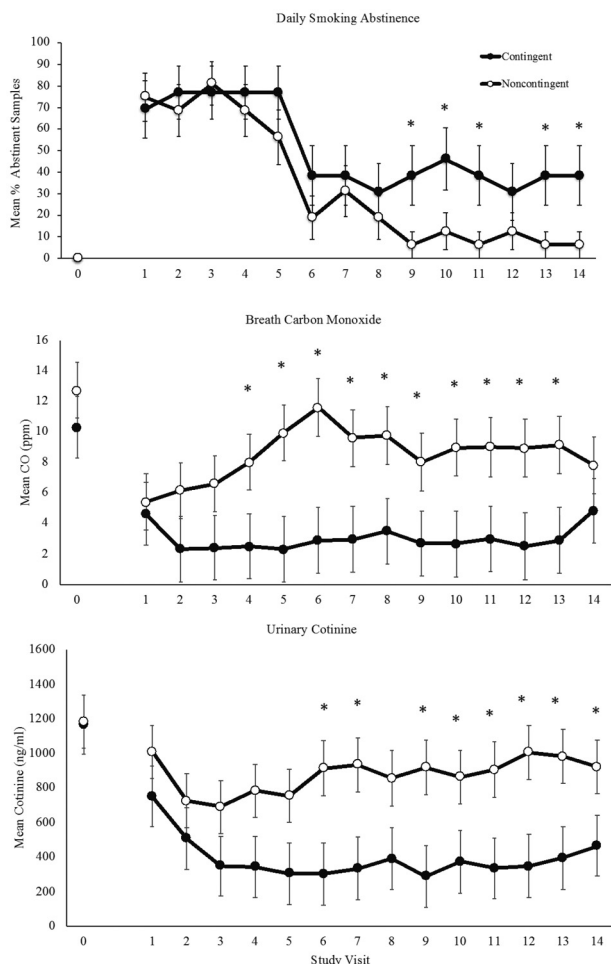
Group differences in breath CO levels over the 14-day study were also day specific ( $F(13, 280) = 1.95$ ,  $p = 0.025$ ; Fig. 1, middle panel). Although both groups presented with elevated CO levels at intake and evidenced a marked decline across the early days of the intervention, participants randomized to the Contingent condition provided significantly lower CO levels on all but four study visits ( $p$ 's  $< 0.05$ ). A similar pattern was seen with urinary cotinine levels. Group differences were day specific ( $F(13, 279) = 2.20$ ,  $p = 0.010$ ), with Contingent participants providing lower cotinine levels than Noncontingent participants at eight of the 14 study visits ( $p$ 's  $< 0.05$ ; Fig. 1, lower panel).

### 4. Discussion

We examined the feasibility and initial efficacy of an incentive-based behavioral intervention for producing initial smoking abstinence among smokers with COPD. Randomization to the Contingent incentive condition produced significantly greater biochemically-verified reductions in smoking among adults diagnosed with COPD. We are aware of only one other published study examining the effects of a incentives-based intervention in smokers with COPD (Crowley et al., 1995). That study was conducted over two decades ago and examined the effects of abstinence-contingent incentives on daily breath CO levels in patients with COPD. While the Contingent incentive intervention was associated with lower CO levels than the Noncontingent control group, the study relied solely on CO monitoring, which can permit low levels of smoking to go undetected. Our use of urinary cotinine provided a more stringent biochemical measure of smoking status. More broadly, our study also adds to the larger treatment development literature with individuals with pulmonary disease in that we did not exclude those with a diagnosis of severe COPD, a trend seen in previous trials (Herland et al., 2005). In the present study, 38% of participants met clinical criteria for severe or very severe COPD.

Several limitations of this study should be noted. First, this was a brief pilot study with a limited duration (i.e., 14 days) and sample size ( $n = 29$ ). Considering these promising initial outcomes, subsequent studies should employ longer durations and larger sample sizes to evaluate the generality of our initial findings. Second, given the brief duration of the intervention, we did not assess changes in COPD health and respiratory function and rather maintained a primary focus on generating and evaluating smoking abstinence. However, future studies over longer durations should evaluate whether experimentally-induced smoking abstinence is associated with improvements in pulmonary health outcomes. Finally, while participants in the Contingent condition demonstrated greater reductions in smoking compared to Noncontingent control participants, few achieved complete smoking abstinence. This is consistent with findings from the one other trial on this topic and supports the notion that this group is a treatment-resistant population who struggles to maintain smoking abstinence (Hoogendoorn et al., 2010; Wagena et al., 2005; Crowley et al., 1995).

In summary, smokers with COPD are an important and costly clinical population in urgent need of more effective smoking cessation interventions. Results from this randomized pilot study support the potential efficacy of a behavioral intervention for reducing cigarette smoking in this difficult-to-treat group. Further research efforts should



**Fig. 1.** Mean daily smoking abstinence (upper panel), mean breath carbon monoxide (CO) levels (middle panel), and mean urinary cotinine levels (lower panel) presented across consecutive study visits during the 14-day study. Abstinence was defined as a CO  $\leq$  6 ppm during Study Days 1–5 and cotinine  $\leq$  80 ng/ml for Days 6–14. Data are presented for Contingent (filled symbols) and Noncontingent (open symbols) experimental conditions. Error bars represent SEM. Group  $\times$  time interactions were significant for all three outcomes ( $p$ 's < 0.05); asterisks indicate significant group differences ( $p$  < 0.05).

seek to promote and evaluate longer-term abstinence and its impact on respiratory function.

**Author disclosures**

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**Contributors**

- Design and conduct of the study:* Sigmon.
- Data collection:* Ochalek, Meyer, Miller, Streck.
- Data analysis:* Badger.
- Manuscript preparation:* Sigmon, Streck.
- Manuscript review and approval:* Badger, Dixon, Higgins, Meyer, Miller, Ochalek, Sigmon, Streck, Teneback.

**Conflicts of interest**

There are no conflicts of interest to declare.

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**References**

Anthonisen, N.R., Skeans, M.A., Wise, R.A., Manfreda, J., Kanner, R.E., Connett, J.E., 2005. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann. Intern. Med.* 142 (4), 233–239. <http://dx.doi.org/10.7326/0003-4819-142-4-200502150-00005>.

Crowley, T.J., Macdonald, M.J., Walter, M.I., 1995. Behavioral anti-smoking trial in chronic obstructive pulmonary disease patients. *Psychopharmacology* 119 (2), 193–204.

Davis, D.R., Kurti, A.N., Skelly, J.M., Redner, R., White, T.J., Higgins, S.T., 2016. A review of the literature on contingency management in the treatment of substance use disorders, 2009–2014. *Prev. Med.* 92, 36–46. <http://dx.doi.org/10.1016/j.ypmed.2016.08.008>.

Dunn, K.E., Sigmon, S.C., Thomas, C.S., Heil, S.H., Higgins, S.T., 2008. Voucher-based contingent reinforcement of smoking abstinence among methadone-maintained patients: a pilot study. *J. Appl. Behav. Anal.* 41 (4), 527–538.

van Eerd, E.A.M., van Rossem, C.R., Spigt, M.G., Wesseling, G., van Schayck, O.C.P., Kotz, D., 2015. Do we need tailored smoking cessation interventions for smokers with COPD? A comparative study of smokers with and without COPD regarding factors associated with tobacco smoking. *Respir Int Rev Thorac Dis.* 90 (3), 211–219. <http://dx.doi.org/10.1159/000398816>.

Fagerström, K., 2012. Determinants of tobacco use and renaming the FTND to the Fagerstrom Test for Cigarette Dependence. *Nicotine Tob Res Off J Soc Res Nicotine Tob.* 14 (1), 75–78. <http://dx.doi.org/10.1093/ntr/ntr137>.

GOLD, 2017. GOLD 2017 Global Strategy for the Diagnosis, Management and Prevention of COPD. Glob Initiat Chronic Obstr Lung Dis - GOLD. <http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/> (Accessed February 9, 2018).

Herland, K., Akselsen, J.-P., Skjongsberg, O.H., Bjermer, L., 2005. How representative are clinical study patients with asthma or COPD for a larger “real life” population of patients with obstructive lung disease? *Respir. Med.* 99 (1), 11–19.

Higgins, S.T., Silverman, K., Heil, S.H., 2008. Contingency Management in Substance Abuse Treatment. Guilford Publications, New York, NY.

Higgins, S.T., Washio, Y., Heil, S.H., et al., 2012. Financial incentives for smoking cessation among pregnant and newly postpartum women. *Prev. Med.* 55 (Suppl), S33–S40. <http://dx.doi.org/10.1016/j.ypmed.2011.12.016>.

Hoogendoorn, M., Feenstra, T.L., Hoogenveen, R.T., Rutten-van Mölken, M.P.M.H., 2010. Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD. *Thorax* 65 (8), 711–718. <http://dx.doi.org/10.1136/thx.2009.131631>.

Jamal, A., 2016. Current cigarette smoking among adults — United States, 2005–2015. *MMWR Morb. Mortal. Wkly Rep.* 65. <http://dx.doi.org/10.15585/mmwr.mm6544a2>.

Jiménez-Ruiz, C.A., Masa, F., Miravittles, M., et al., 2001. Smoking characteristics: differences in attitudes and dependence between healthy smokers and smokers with COPD. *Chest* 119 (5), 1365–1370.

Sigmon, S.C., Patrick, M.E., 2012. The use of financial incentives in promoting smoking cessation. *Prev. Med.* 55 (Suppl), S24–S32. <http://dx.doi.org/10.1016/j.ypmed.2012.04.007>.

Sobell, L.C., Sobell, M.B., 1992. Timeline Follow-Back. In: *Measuring Alcohol Consumption*. Humana Press, Totowa, NJ, pp. 41–72. [http://dx.doi.org/10.1007/978-1-4612-0357-5\\_3](http://dx.doi.org/10.1007/978-1-4612-0357-5_3).

Tønnesen, P., 2013. Smoking cessation and COPD. *Eur Respir Rev Off J Eur Respir Soc.* 22 (127), 37–43. <http://dx.doi.org/10.1183/09059180.00007212>.

U.S. Department of Health and Human Services, 2014. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General, 2014. vol. 944 SurgeonGeneral.Gov. Office on Smoking and Health: Centers for Disease Control and Prevention. <http://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html> (Accessed May 22, 2016).

USDHHS, 2017. Health, United States, 2016. National Center for Health Statistics.

Wagena, E.J., Knipschild, P.G., Huijbers, M.J.H., Wouters, E.F.M., van Schayck, C.P., 2005. Efficacy of bupropion and nortriptyline for smoking cessation among people at risk for or with chronic obstructive pulmonary disease. *Arch. Intern. Med.* 165 (19), 2286–2292. <http://dx.doi.org/10.1001/archinte.165.19.2286>.

Wu, J., Sin, D.D., 2011. Improved patient outcome with smoking cessation: when is it too late? *Int J Chron Obstruct Pulmon Dis.* 6, 259–267. <http://dx.doi.org/10.2147/COPD.S10771>.