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Corresponding Author: Dr. Sara Weidberg, PhD

Corresponding Author's Institution: University of Oviedo

First Author: Sara Weidberg, PhD

Order of Authors: Sara Weidberg, PhD; Guillermo Vallejo-Seco; Alba González-Roz; Ángel García-Pérez; Roberto Secades-Villa

Cover Letter

Sara Weidberg, Ph.D.
Department of Psychology. University of Oviedo.
Plaza Feijóo s/n, 33003, Oviedo, Spain.

February 15th, 2018

Dr. Marcantonio M. Spada
Editor-in- Chief
Addictive Behaviors

I wish to submit the revised version of the manuscript "In-treatment cigarette demand among treatment-seeking smokers with depressive symptoms" (Ms. Ref. No.: ADDICTBEH-D-17-00693) for publication in the journal Addictive Behaviors. The title has been slightly modified so as to adapt it to one of the reviewers' requirements. The authors are very grateful for all the suggestions made the reviewers, and have modified the manuscript accordingly. We have addressed all the comments made by the reviewers, and all the changes in the manuscript are highlighted in yellow. We feel that these modifications have considerably improved the manuscript and contributed to increasing its potential impact.

As in the initial submission, the authors confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere. All authors have been personally and actively involved in substantive work leading to the report, and will hold themselves jointly and individually responsible for its content. Because of his contribution to this revised version, we would like to add Ángel García-Pérez M.A. as a co-author of the manuscript. The order of the authors has been modified due to their contribution to this current version. Lastly, all authors declare that they do not have any financial relationship with the funding sources that sponsored the present study.

I testify to the accuracy of the above on behalf of all the authors.

Please address all correspondence concerning this manuscript to me at weidbergsara.uo@uniovi.es

Thank you for your consideration of this manuscript.

Sincerely,

Sara Weidberg, Ph.D.

***Response to Reviewers**

Reviewer #1: Overview: This is a study examining the relation between within-treatment changes in urinary cotinine levels (as a measured of decreased smoking) and indices of smoking demand, as measured by the Cigarette Purchase task. Data are drawn from an 8-week randomized clinical trial (N=92) comparing CBT + BA to CBT + BA + CM in smokers with depressive symptoms. Overall, this is a timely paper that contributes to a growing literature on the utility of this behavioral economic measure (CPT) for understanding the etiology and maintenance of smoking, as well as potential policy/intervention effects on smoking. Reading through the paper, I found the framework (e.g., the structure of the aims) somewhat unexpected. Specifically, I would have expected the primary research question to be a comparison of the effects of the two treatment arms on the indices of demand from the CPT. Following that, the examination of relations between decreased cotinine and demand seems secondary, perhaps framed as the reduction in cotinine being a potential mediator of the effect of treatment on reducing demand. I am very reluctant to second-guess researchers' framing of their aims, but wanted to offer that the alternative framework described above would have flowed better, from my perspective.

We thank the Reviewer 1 for highlighting the strengths of our study. We have also followed his/her suggestion regarding the organization of the objectives (see page 4, third paragraph). Consequently, we have altered the order in the presentation of the main findings (see subsections 3.2. and 3.3 of the Results section). The results in section 3.2 are now related with the effects of treatment condition on cigarette demand over time, while those in section 3.3 concern the effects of smoking consumption in cigarette demand over time. Lastly, these modifications have also altered the order that the findings appear in the Discussion section.

Below are some further suggestions for the authors' consideration. They appear in the order in which they arise in the manuscript.

1) Introduction: The introduction provides a succinct and focused review of relevant work involving the CPT in smoking trials. On p. 4, the authors' reference to the Smith et al. (2017) study is used to set up the current study's focus on nicotine reduction effects on cigarette demand. But the description of this study does not fully reflect the study design nor conclusions - these need to be more accurately described. The point of the Smith et al. study was not that nicotine reduction per se reduced demand, rather it was that six weeks' experience smoking research cigarettes with very low levels of nicotine was associated with reduced demand for those specific cigarettes. It is a test of the manipulation of nicotine content in cigarettes, not a test of how much nicotine participants were actually exposed to at the end of six weeks, and how any reduction related to reduced demand. The bottom line is, the Smith study tested the effects of an intervention (nicotine in cigarettes) on demand, and the current tested the effects of different interventions (CBT, BA, and CM) on demand - they each contribute something important, but the current study does not address limitations in the Smith study directly as the authors assert - their foci are different.

After carefully reading this comment and the Smith et al. (2017) study, we completely agree with the Reviewer 1 that the aims of the Smith et al. (2017) study and the present one are different. We have modified both the description of the Smith et al. (2017) study and stated that they conducted an experimental study in which participants received their usual brand of cigarettes (control condition) or investigational ones with lower nicotine content during a 6-week period. We have also changed the main result of the Smith et al. (2017) study by stating that, compared to the control condition, participants who smoked investigational cigarettes reduced their cigarette demand for those specific cigarettes (see page 4, first paragraph).

As the purpose of our study differs from the Smith et al. (2017) research, we have also modified the wording of the general aim (see last paragraph of the introduction section, page 4).

2) Methods: p. 8. Although the CM protocol has been described elsewhere, the basic information should be presented in the manuscript. At a minimum, what was the

schedule of incentives over the 8 weeks and how much did participants earn on average in this condition?

Following the Reviewer´s suggestion we have added further information on the CM protocol (see page 9, first paragraph). It now includes a description on the schedule of incentives we used and the mean money earned in vouchers at the end of treatment.

3) All other methods, including data calculations and analyses, are clearly described in sufficient detail. Results, similarly, were clearly described and sufficiently detailed. However, one relevant aspect of the parent study that is not disclosed in this paper is the nature of the intervention effects on smoking (and cotinine levels). Have these results been published? Were there significant effects of CBT+BA+CM (vs. CBT+BA) on smoking/cotinine? If the authors hypothesize that the mechanism accounting for treatment effects on reduced demand is reduction in smoking (cotinine), then the results of the main trial are relevant here. Further, descriptive data on percentage of participants who met abstinence criteria across the trial would help to clarify the outcomes and demand data. It is not clear until page 20 that only a small percentage of participants remained smoking by week 8.

We thank the Reviewer 1 for this suggestion. In order to meet this Reviewer's requirement, the current version of the manuscript includes a new table showing cotinine levels across sessions by treatment condition (see Table 2, page 14). This table also shows the percentage of abstinent participants (i.e., cotinine levels <80 ng/ml) by treatment condition.
On the other hand, we would like the Reviewer to note that the percentage he/she was mentioning does not correspond with the proportion of participants who are smoking at the end of treatment (eighth week). Instead, it indicates the percentage of participants whose demand data could be used for obtaining elasticity in the last mid-week session (seventh week), which is 8.7%. In this session, smokers in the CBT + BA condition were 29.8%, and 31.1 % in the CBT + BA + CM condition (see complementary data regarding abstinence rates in Table 2).

4) Discussion. The discussion at the top of p. 20, noting the effect of tax increases on cigarette demand misses the opportunity to relate this work to the CM intervention, which essentially increases the "cost" of smoking by providing monetary incentives for abstinence. If an escalating schedule of incentives was used (not described in the paper) then the cost of smoking would increase over the course of the 6-week trial. This could explain the effects of CM on intensity at the end of 6-weeks but not earlier.
In sum, this is a well-implemented and timely study that substantially contributes to an emerging literature relating behavioral economics to smoking outcomes. Some changes to the write-up could potentially increase its clarity and impact.

We agree that the escalating schedule of incentives used in this CM protocol could act as a potential mechanism accounting for intensity reductions over the course of treatment. Accordingly, we have now argued that the cost posed by incentives might have led patients to reduce their self-reported cigarettes at cost zero (i.e., intensity). Please consider that this information is now included in the second paragraph of the discussion section due to it fitting better here (see page 23). The Reviewer also notes that the increasing magnitude of reinforcement might be operating over intensity reductions at the end of treatment. The fact that the intensity of demand decreased as time passes, but also early in treatment, suggests that CM is also impacting patients' expectations to receive vouchers, thereby accounting for large reductions in cotinine levels (i.e., weeks 2-4), even before the quit day.

Reviewer #2: Review of "Impact of smoking reduction on in-treatment cigarette demand among treatment-seeking smokers with depressive symptoms"

This manuscript examined whether decreases in smoking intake impacted in-treatment cigarette demand, as measured by the Cigarette Purchase Task (CPT; MacKillop et al., 2008), which estimates the number of cigarettes that one is willing to purchase across

escalating prices). The study examined 92 treatment-seeking daily smokers with depressive symptoms who received either CBT+BA or CBT+BA+CM. Results indicated that cotinine levels were significantly related to cigarette demand, decreases in cotinine levels were significantly related to cigarette demand reductions, and those in CBT+BA+CM had higher reductions in cigarette demand across sessions than those in CBT+BA.

The manuscript is well written and cogent. Strengths of the manuscript include its topic area, use of biochemical verification, and examination and manipulation of cigarette demand without requiring smoking. The statistical approach appears generally defensible. Limitations include lack of information on the CPT task itself, questions regarding the generalizability of the sample to smokers without depressive symptoms, some lack of information about procedures and methods, and lack of data/results on the treatment groups.

We thank the Reviewer 2 for underlining the strengths of our study. As the Reviewer may read in the specific issues below, in the current version we have provided detailed information on the way the CPT was administered. We have also included the instructional set for the task. The Methods section now includes further information regarding the study procedure and methods as well as a new table showing cotinine levels across sessions by treatment condition.

Some specific issues to be addressed:

1. A brief mention of any differences between DSM-IV Nicotine Dependence and DSM-5 Tobacco Use Disorder might be helpful to assure the reader that the results would be consistent using DSM-5 criteria.

We appreciate the Reviewer´s suggestion. Note that on page 9 (third paragraph), we have indicated that the more recent SCID version for tobacco use disorder (based on DSM-V criteria) was not available at the time of the study onset. We also briefly mentioned the main differences between the DSM-IV-TR and the DSM-V. The fact that only a few changes were made for the diagnosis of tobacco use disorder suggest that no significant differences exist. Please consider that the FTND was also used to assess for nicotine dependence levels, thus making comparison with prior research possible.

2. On p. 5 the authors state that they excluded participants with a "current severe psychiatric disorder other than depression." No information is provided on how this was determined and how "severe" is operationally defined. One might assume that all psychiatric disorders were assessed with the SCID-CV as noted on p. 9, but it states there that current and past depression were assessed (doesn't specifically state that other diagnoses were assessed).

We thank the Reviewer this suggestion. In the revised version of the manuscript, we have stated that when overlapping symptoms existed, the therapist used the appropriate modules of the SCID-I to make a differential diagnosis in order to ensure the current depressive symptomatology is no better accounted for by another psychiatric disorder (see page 6, first paragraph).

3. On p. 5, it would be helpful to the reader to indicate that > = 14 on the BDI reflects mild severity or higher.

This information is now stated in the Participants subsection (see page 5, second paragraph).

4. No information is provided on procedurally how or when the CPT was administered and by whom. This might be useful considering that the treatment sessions are described as 90 minutes in duration, which seems rather long given most traditional treatment sessions are 60 minutes.

We thank the Reviewer for this suggestion. The revised version of the manuscript now states that the participants completed the CPT at the beginning of all midweek sessions, and that instructions on how to complete it were provided in each session. Therapists administered the

CPT to the participants and were present throughout to answer questions (see third paragraph, page 10).
We have now stated that clinical sessions lasted 90 min while midweek sessions only lasted 30 minutes (as they were only scheduled for completing the CPT and assessing cotinine levels) (see third paragraph, page 6). As the Reviewer suggests, this time is rather long compared to traditional treatment sessions. Due to the incorporation of BA in the CBT protocol we extended the treatment duration.

5. The justification on p. 8 for using only midweek cotinine specimens wasn't clear nor compelling. Have the authors analyzed the data including all specimens, and if so, what does it reveal?
The present version of the study includes a new table showing cotinine levels across sessions as a function of treatment condition (see Table 2, page 14). This table includes cotinine levels not only from the midweek sessions (designated as "b" sessions) but also from the clinical sessions. As the Reviewer may read in subsection 3.1 of the results (page 13), cotinine values were higher across sessions among participants who received CBT + BA when compared to those who received CBT + BA + CM. Specifically, significant differences by group were found in sessions 2b, 3, 3b, 4, 4b, 5 and 6. The percentage of participants whose cotinine levels were < 80 ng/ml was higher in the CBT + BA + CM group than in the CBT + BA group, although differences were only significant in session 5. Despite all cotinine values now being included in Table 2, it is unsuitable to analyze cotinine values from the clinical sessions in combination with cigarette demand because participants did not complete the CPT in the clinical sessions (they only did so in the midweek sessions). It would not make sense to analyze the association between cigarette demand and cotinine levels that were assessed several days before participants completed the CPT each week. For this reason, cotinine values from the clinical sessions are now presented in Table 2 but they were not entered in the likelihood-based mixed effects regression models (MRM) that examined cigarette demand in combination with cotinine.

6. The authors cite other studies rather than describe the CPT instructional set on p. 9, likely out of desire to conserve manuscript space. I would instead encourage the authors to at least briefly describe the instructional set and provide some detail, given that their study rests almost entirely on that measure.
Following the Reviewer's recommendation, the instructional set of the CPT is now provided in the measures subsection (pages 10 and 11).

7. It was unclear whether the statistical analyses were intent-to-treat analyses—please confirm.
This is now confirmed in the Statistical Analyses subsection (page 11, third paragraph).

8. There is no information on the number of participant data points that were excluded when the data did not fit the assumed exponential curve (p. 11).

We apologize for this mistake. As the Reviewer may now read, 250 data points did not fit the exponential curve (page 12, second paragraph).

9. The labels on the figures are so small as to be nearly illegible; please enlarge the fine print.

For legibility, we have completed the required amendments in the print size.

10. In Tables 2-6, I assume that "LB" refers to baseline—if so, it might make more sense to use "BL" instead for clarity.
We apologize for this error. We have replace "LB" for "BL" in Tables 3-7 (2-6 in the original version of the manuscript).

11. The authors rather tantalizingly mention that reductions in cotinine levels were significantly higher in smokers who were in the CM group but that they did not report

results for brevity concerns. Again, the manuscript would be strengthened by at least briefly mentioning results of the parent study as it relates to the current study's impact on the field.

To address this issue, the current version of the manuscript includes a new table showing cotinine levels across sessions as well as the percentage of participants whose cotinine specimens were <80 ng/ml. The information is provided by treatment condition (see Table 2).

12. The authors cite Amlung et al. on p. 21 regarding no differences between hypothetical and actual purchase tasks. However, the Amlung study was on alcohol, not on cigarettes, and thus it may or may not be translatable to smoking. It would be important to mention that as a caveat.

After considering the Reviewer´s suggestion, we decided to remove Amlung et al.'s study and cite a study conducted in the population of cigarette smokers instead (Wilson, Franck, Koffarnus, & Bickel, 2016). These authors concluded that with the exception of elasticity of demand, no substantially differences between the hypothetical and actual purchase tasks exist (see page 25, second paragraph).

13. The authors conclude on p. 22 that nicotine fading should be considered an effective strategy for smoking cessation interventions. However, based on this manuscript, the parent study (the RTC) did not specifically include nicotine fading (operationally defined as changing cigarette brands gradually to those with a lower nicotine content) in the treatment protocol. If it did, then that should be included in the manuscript. See #12.

All the treatment protocols in this study included nicotine fading as the main component of CBT. Nicotine fading is now described in the treatment interventions subsection (page 8, first paragraph).

References

Smith, T. T., Cassidy, R. N., Tidey, J. W., Luo, X., Le, C. T., Hatsukami, D. K., & Donny, E. C. (2017). Impact of smoking reduced nicotine content cigarettes on sensitivity to cigarette price: further results from a multi-site clinical trial. *Addiction, 112*, 349-359. doi: 10.1111/add.13636

Wilson, A. G., Franck, C. T., Koffarnus, M. N., & Bickel, W. K. (2016). Behavioral Economics of Cigarette Purchase Tasks: Within-Subject Comparison of Real, Potentially Real, and Hypothetical Cigarettes. *Nicotine Tobacco Research, 18*(5), 524-530. doi: 10.1093/ntr/ntv154

Highlights:

- We assess if decreases in smoking intake impact in-treatment cigarette demand.
- Smokers who received Contingency Management showed higher decreases in intensity.
- Cotinine levels were positively related to cigarette demand.
- In-treatment cotinine decreases were associated with cigarette demand reductions.
- Nicotine intake reductions decreased in-treatment cigarette demand.

In-treatment cigarette demand among treatment-seeking smokers with depressive symptoms

Weidberg, S.[a], Vallejo, G. [a], González-Roz, A.[a], García-Pérez, Á.[a] & Secades-Villa, R. [a]

[a]Department of Psychology. University of Oviedo. Plaza Feijóo s/n, 33003, Oviedo, Spain

Corresponding author:

Sara Weidberg

Department of Psychology, University of Oviedo, Plaza Feijóo, s/n, 33003 Oviedo, Spain.

E-mail: weidbergsara.uo@uniovi.es

Fax: +34985104141

Abstract

Introduction: Despite previous evidence supporting the use of the Cigarette Purchase Task (CPT) as a valid tool for assessing smoking reinforcement, research assessing how environmental changes affect CPT performance is scarce. **Aims:** This study addressed for the first time the differential effect of treatment condition [Cognitive Behavioral Treatment (CBT) + Behavioral Activation (BA) versus CBT + BA + Contingency Management (CM)] on cigarette demand among treatment seeking smokers with depressive symptoms. It also sought to assess whether reductions in smoking consumption arranged over the course of an intervention for smoking cessation impact on in-treatment cigarette demand. **Method:** Participants were 92 smokers with depressive symptoms from a randomized clinical trial that received eight weeks of either CBT + BA or CBT + BA + CM. Individuals completed the CPT 8 times; the first during the intake visit and the remaining 7 scheduled once a week in midweek sessions. Cotinine samples were collected in each session. **Results:** Participants receiving CBT + BA + CM showed higher reduction in cigarette demand across sessions than participants receiving CBT + BA, although this comparison was only significant for the intensity index ($p = 0.004$). Cotinine was positively related to cigarette demand (all p values < 0.001), although this association became less prominent across sessions. In-treatment cotinine decreases were associated with demand reductions (all p values < 0.001), but this association was not significant for elasticity. **Conclusions:** Reductions in nicotine intake arranged over the course of an intervention for smoking cessation impact in-treatment cigarette demand.

Keywords: cigarette purchase task; demand indices; smoking reduction; treatment.

1. Introduction

Behavioral Economics is a translational area of research that assesses how changes in reinforcer costs affect reinforcer consumption (Hursh & Roma, 2013). One assessment used in the addiction research that takes this approach is the Cigarette Purchase Task (CPT) (MacKillop et al., 2008), which estimates the number of cigarettes that a given smoker is willing to purchase across a range of escalating prices. From these data, it is possible to plot a demand curve characterizing changes in cigarettes consumption as a function of price (Koffarnus, Franck, Stein, & Bickel, 2015). Because the CPT allows manipulation of cigarette demand without asking participants to smoke, it has been increasingly used to assess smoking reinforcement at the expense of basic operant laboratory measures that incur greater costs in terms of time (frequent, long-duration sessions) and money (participant compensation) (Wilson, Franck, Koffarnus, & Bickel, 2016).

Previous research establishes CPT as a valid measure of cigarette reinforcement, as there is robust evidence of its convergent (Few, Acker, Murphy, & MacKillop, 2012; Secades-Villa, Pericot-Valverde, & Weidberg, 2016; Secades-Villa, Weidberg, Gonzalez-Roz, Reed, & Fernandez-Hermida, 2017) and incremental (Chase, MacKillop, & Hogarth, 2013) validity. CPT has also proven its predictive validity, since performance in the task is a robust predictor of treatment outcome (Mackillop et al., 2016; Secades-Villa et al., 2016).

Assessing whether certain environmental variables impact CPT performance have important implications for tobacco regulation and control strategies. Nevertheless, research assessing CPT changes is scarce. Grace, Kivell, & Laugesen (2015a) found that smokers were more sensitive to increases in cigarette price after a tobacco tax

increase in New Zealand. Similarly, Smith et al. (2017) conducted an experimental study in which participants received their usual brand of cigarettes (control condition) or investigational ones with lower nicotine content during a 6-week period. The results of this study showed that, compared to the control condition, participants who smoked investigational cigarettes reduced their cigarette demand for those specific cigarettes. Furthermore, administering cigarettes with lower nicotine content increased the number of participants who reported that they would quit smoking if the study cigarettes were the only ones available for purchase. Nevertheless, the fact that smokers in this study had no intention to quit precludes these findings from being generalized to treatment seeking smokers. Moreover, Smith et al. (2017) rely solely upon self-reported nicotine intake, which is subject to response bias as opposed to a biochemical verification of smoking status (Connor Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009).

Only two studies to date found reductions in cigarette demand in smokers after a nicotine replacement therapy (Murphy et al., 2017; Schlienz, Hawk, Tiffany, O'Connor, & Mahoney, 2014), but the impact of psychological interventions for smoking cessation on cigarette demand remains to be addressed.

This is the first study with the aim of assessing in-treatment changes in cigarette demand among a sample of adult smokers who are motivated to quit. The specific objectives of the study are: 1) to analyze the differential effect of treatment condition [Cognitive Behavioral Treatment (CBT) + Behavioral Activation (BA) versus CBT + BA + Contingency Management (CM)] in cigarette demand over time, and 2) to explore whether reductions in smoking consumption arranged over the course of an intervention

for smoking cessation impact in-treatment cigarette demand among smokers with depressive symptoms.

2. Materials and method

2.1.Participants

Participants consisted of a subset of 92 treatment seeking smokers (72.8 % women) with depressive symptoms who enrolled in a randomized controlled trial for smoking cessation (NCT03163056) at the Addictive Behaviors Clinic of the University of Oviedo, Spain. The purpose of that trial was to assess whether adding a both a CM and a BA component to a CBT intervention would significantly increase smoking cessation rates and ameliorate depressive symptoms among treatment-seeking smokers with depression. Individuals were recruited using flyers and advertisements posted around the local community. When potentially eligible subjects contacted the clinic via phone or e-mail, they were scheduled for an in-person appointment. Inclusion criteria for this study were: (1) being aged 18 or over, (2) meeting the diagnostic criteria for nicotine dependence according to the Diagnostic and Statistical Manual of Mental Disorders (4^{th} ed., text rev; DSM-IV-TR) (American Psychiatric Association, 2000) assessed by the structured Clinical Interview for DSM-IV (SCID-I), 3) having smoked 10 or more cigarettes per day for the last year, and 4) meeting criteria for current unipolar major depression disorder according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev; DSM-IV-TR), and/or scoring ≥ 14 on the Beck Depression Inventory (Beck, Steer, & Brown, 1996), which is indicative of at least mild depressive symptomatology. Exclusion criteria were: (1) being diagnosed with a current severe psychiatric disorder other than depression (i.e., schizophrenia, bipolar disorder), (2) currently receiving other treatment for smoking cessation at the time of intake

assessment, and (3) meeting criteria for abuse and/or dependence on a substance other than nicotine. When overlapping symptoms existed, the therapist used the appropriate modules of the SCID-I to make a differential diagnosis and thereby ensured that the current depressive symptomatology was not better accounted for by another psychiatric disorder.

This study was approved by the International Review Board of the University of Oviedo and informed consent was obtained from all participants before the study initiation.

2.2.Procedure

2.2.1. Treatment Interventions

Participants were assigned to the CBT+BA group (n = 47) or to the CBT+BA+CM group (n = 45) in accordance with a digitally randomized list. Both treatment interventions were developed by staff members at the institution, holding either a masters or PhD level qualification, and who were previously trained in the specific protocols. Both interventions were implemented in a group-based format of a maximum of four patients over an 8 week period. Individuals received one therapy session once a week and were also asked to attend midweek sessions (hereinafter referred as "b" sessions) to collect biochemical measures. The maximum duration of therapy and midweek sessions was 90 and 30 minutes, respectively. For all treatment conditions, the quit day was set 48 hours before the fifth session. Table 1 shows participants' baseline measures by treatment condition. No significant differences between the two treatment conditions were observed.

Table 1 Descriptive data regarding baseline measures and cigarette demand indices as a function of treatment condition (N = 92)

Measures	CBT+BA (n=47)	CBT+BA+CM (n=45)	*p* value
Sociodemographic characteristics			
Age[a]	51.79 ± 9.71	53.07 ± 8.59	.506
Gender (% female)	70.2	75.6	.733
Marital status (% married)	44.7	66.7	.100
Education (%)			.911
< High school	14.9	17.8	
High school	53.2	53.3	
≥ University	31.9	28.9	
Income (%)			.107
<600-900 €	43.9	57.1	
901-1500 €	22	28.6	
1501-2400 €	34.1	14.3	
BDI-II[a]	26.60 ± 10.05	30.33 ± 8.66	.060
Smoking-related measures			
Cigarettes per day[a]	23.68±8.53	20.98±7.23	.104
Years of smoking[a]	32.64 ± 10.71	32.31 ± 9.31	.876
FTND[a]	6.79 ± 1.90	6.04 ± 1.98	.069
SCID-I[a]	5.73 ± 1.16	5.49 ± 1.27	.343
Cotinine (ng/ml)[a]	2570.40 ± 1352.69	2526.94 ± 1067.51	.866
CPT demand indices			
Breakpoint[a]	15.76 ± 22.68	19.11 ± 28.76	.449
Intensity[a]	22.56 ± 8.47	20.89 ± 6.66	.302
Elasticity[a]	0.0066 ± 0.0056	0.0080 ± 0.0074	.311
Omax[a]	20.59 ± 23.87	16.11 ± 22.87	.365
Pmax[a]	6.66 ± 10.93	8.36 ± 12.67	.497

[a] = Means ± SD/independent-samples t-tests; BDI-II = Beck Depression Inventory-II FTND = Fagerström Test for Nicotine Dependence; SCID-I = Structured Clinical Interview for DSM-IV; ng/ml = nanograms/milliliter; CPT = Cigarette Purchase Task.

2.2.1.1. CBT+ BA

This intervention included both CBT and BA strategies for smoking cessation and depression management. The CBT component has been previously described and can be found elsewhere (Secades-Villa, García-Rodríguez, López-Núñez, Alonso-Pérez, & Fernández-Hermida, 2014). The core component of the CBT was nicotine fading.

From the first to the fourth treatment week, patients were asked to reduce their nicotine consumption by 30% a week. To achieve this decrease, a maximum number of cigarettes per day and specific cigarette brands with lower nicotine content were advised. The BA component consisted of an adaptation from MacPherson, Collado, Lejuez, Brown, & Tull (2016) and was implemented from the first session. It included the following strategies: treatment rationale, psychoeducation on the association between smoking and depression, and the identification of life areas, values and activities for the generation of meaningful, reinforcing and positive activities. Each week, patients were encouraged to engage in and monitor each in-session planned activity. In addition, a supportive network was created through the formation of contracts during cessation efforts.

Cotinine specimens were collected twice a week (see Table 2 for cotinine data across sessions). One of the measures coincided with the weekly therapy session and the other was scheduled midweek between sessions. Given that participants completed the CPT only once a week (coinciding with the midweek session), only cotinine specimens from these sessions were used to analyze the association between smoking consumption and cigarette demand. Thus, a total of 8 cotinine samples per participant (one from the intake session and the remaining from the 7 midweek sessions) were considered in combination to the demand data. Participants were informed of their urinalysis results (cotinine) immediately after submitting their specimens, but received no type of incentive for reinforcing abstinence.

2.2.1.2. CBT+ BA + CM

Individuals assigned to this treatment condition were provided with the above treatment protocol, but with the addition of a CM component reinforcing abstinence.

The CM procedure has been previously described (Secades-Villa et al., 2014). The number of sessions and the collection of cotinine samples was the same as in the CBT + BA condition. Patients were presented with vouchers upon proof of abstinence (cotinine levels ≤ 80 ng/ml) from the fifth session (i.e., the first session patients were required to remain abstinent) and onwards. The reinforcement schedule involved an escalating magnitude of reinforcement that began at 10€ (US$ 10.64) voucher for the first abstinent specimen and increased by 5€ (US$ 5.34) for each consecutive negative sample. Maximum possible earnings per patient were 175€ (US$ 190), and the average amount earned in vouchers was 112.11€ (US$ 137.47).

2.3.Measures

Participants completed a brief questionnaire assessing data on sociodemographic variables (e.g., age, sex, educational level, marital status) in addition to various smoking-related measures including cigarettes smoked per day and years of regular smoking.

The Fagerström Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) was used to assess nicotine dependence. The SCID-I based on the DSM-IV-TR criteria (American Psychiatric Association, 2000) was administered to all participants to assess the presence of nicotine dependence. Although there is a more recent version based on the DSM-V, there was no available Spanish adaption of the SCID-VC at the time of the study onset. Nonetheless, with the exception of craving and the increased number of required diagnostic criteria (i.e., 3 rather than 2), no substantially differences with the prior DSM version exist (Hasin et al., 2013).

A BS-120 chemistry analyzer (Shenzhen Mindray Bio-medical Electronics Co. Ltd., Shenzhen, P. R. China) was also used to determine urine cotinine levels through an

homogeneous enzyme immunoassay system. Smoking status was defined as presenting a urinary cotinine sample of ≥ 80 nanograms per milliliter (ng/ml). Participants were considered smokers when they missed an assessment.

Depressive symptomatology was assessed by means of the Beck Depression Inventory-Second Edition (BDI-II) (Beck et al., 1996). The presence of both current and past depression was explored through the Structured Clinical Interview for DSM-IV Disorders (SCID-CV) (First, Spitzer, Gibbon, & Williams, 1996) based on the DSM-IV-TR diagnostic guidelines.

In order to assess changes in cigarette demand, participants completed the CPT 8 times. The first occurred during the intake visit and the remaining 7 were scheduled once a week in the midweek sessions. The task was adapted from MacKillop et al. (MacKillop et al., 2008), and asked participants to estimate how many cigarettes they would smoke across a range of prices. Participants completed the CPT at midweek sessions. Instructions on how to complete this task were provided in each session. Therapists were present to ensure adequate comprehension of the task. The instructional set that participants received was the following (MacKillop et al., 2008):

"Imagine a TYPICAL DAY during which you smoke. The following questions will determine how many cigarettes you would consume if they cost various amounts of money. The available cigarettes are your favorite brand. Assume that you have the same income and savings that you have now and NO ACCESS to any cigarettes or nicotine products other than those offered at these prices. In addition, assume that you would consume cigarettes that you request on that day; that is, you cannot save or stockpile cigarettes for a later date. Please respond to these questions honestly".

Participants were then asked to respond to the following question: "How many cigarettes would you smoke if they were ____ each? at the following 19 prices: €0(free), €0.01, €0.02, €0.05, €0.10, €0.25, €0.50, €1, €2, €3, €4, €5, €10, €20, €50, €100, €250, €500, €1,000. The prices were presented in ascending order.

The CPT generates a demand curve, reflecting the quantitative relationship between demand for cigarettes and escalating price. Five indices are obtained from this task: (1) breakpoint (i.e., the first price at which consumption is zero), (2) intensity of demand (i.e., consumption at the lowest price), (3) elasticity of demand (i.e., sensitivity of cigarette consumption to increases in cost), (4) Omax (i.e., maximum expenditure for cigarettes), and (5) Pmax (i.e., price at which expenditure is maximized). According to MacKillop et al. (2008), breakpoint, intensity, Omax and Pmax were directly obtained from raw values so they do not rely on the fit of the demand equation. Elasticity was obtained through a derived approach by using Hursh and Silberberg's (2008) exponential demand curve equation (described in the statistical analyses section).

2.4.Statistical Analyses

Various descriptive and frequency analyses were carried out in relation to the participants´ baseline characteristics. Comparisons between treatment conditions (CBT + BA; CBT + BA+ CM) in both sociodemographic and smoking-related baseline variables were conducted using chi-squared tests and *t*-tests (two-tailed; after Levene's correction for inequality of variance), as appropriate. All analyses were conducted using an intent-to-treat approach.

Nonlinear regression was used to obtain an R^2 value, indicating the adequacy of the fit of the model to the data. Given that the log of 0 is unidentifiable, the first

instance of zero consumption was replaced with an arbitrary non-zero value (i.e., .01), so they could be entered in the model.

The only derived demand metric, elasticity of demand, was generated by fitting the CPT responses to Hursh and Silberberg's (2008) exponential demand curve equation:

$$\log Q = \log Q0 + k(e^{-\alpha Q0C} - 1) \quad (1)$$

where Q = consumption at a given price; Q0 = derived intensity; α = elasticity (slope of the demand curve); k = range of dependent variable (number of cigarettes); and *C* = reinforcer cost. A fixed value of k = 4 was collapsed for all participants based on the overall mean performance on the CPT. Following the Smith et al. (2017) study, elasticity was obtained through the aforementioned method, except when a participant's data did not fit the assumed exponential curve; that is, when (1) the number of cigarettes smoked increased from one price to the next higher price by > 10 cigarettes and > 100%, (2) R^2 values ≤ 0.20 or (3) participants reported that they would smoke 0 cigarettes at all prices (including $0.00) or all prices > $0.00. Excluding participants in category (3) eliminates those who were most impacted by a reduction in nicotine content. A total of 250 data points did not fit the exponential curve due to category (3) in all cases. Hence, for these participants results focus upon empirical indices.

Outliers for demand indices were defined as Z > 3.29 and were winsorized to one unit above the next highest non-outlying value (Tabachnick & Fidell, 2006). Sixty-seven outliers were identified and recoded following this procedure.

Likelihood-based mixed effects regression models (MRM) with repeated measures (Singer & Willett, 2003) were used to analyze the association between reductions in smoking consumption (assessed by cotinine levels) and cigarette demand over time. This analytic approach was also applied to determine whether changes in

cigarette demand differed by treatment condition. The MRM models allows us to analyze missing data from longitudinal randomized trials (Vallejo, Fernández, Livacic-Rojas, & Tuero-Herrero, 2011). As both CPT and cotinine values presented high inter-subject variability, all analyses were conducted after performing logarithmic transformations of such variables.

Descriptive and frequency analyses were conducted with SPSS version 22.0 (SPSS Inc., Chicago IL, USA) and the confidence level was 95%. The GraphPad Prism® macro available online via the Institute for Behavioral Resources (http://www.ibrinc.org) was used for all Equation 1 fits. The dataset was analyzed using MRM with maximum likelihood (REML) estimation implemented in SAS PROC MIXED version 9.4. (SAS Institute, Cary, NC).

3. Results

3.1.Cotinine levels by treatment condition

Table 2 shows comparisons in cotinine levels by treatment condition in both clinical and midweek sessions. Cotinine values were lower across the intervention among participants who received CBT + BA + CM when compared to those who received CBT + BA. Specifically, significant differences by group were found in sessions 2b, 3, 3b, 4, 4b, 5 and 6 (all p values < .048). The percentage of participants presenting cotinine levels < 80 ng/ml was higher in the CBT + BA + CM condition than in the CBT + BA, although differences were only significant in session 5 (p = .038).

Table 2. Cotinine levels across sessions by treatment condition (N = 92)

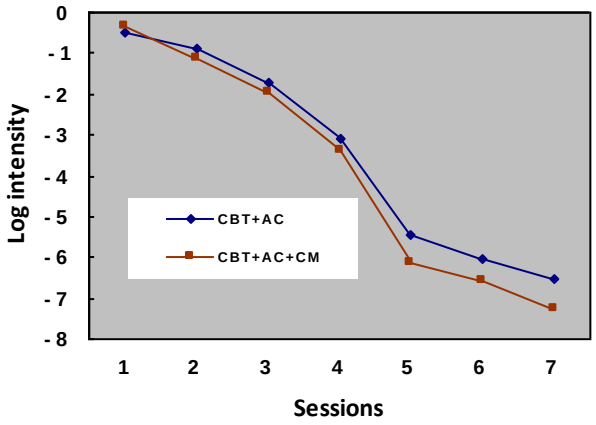
	CBT + BA (n=47)		CBT + BA + CM (n=45)		*p* value	
Session	Mean ± SD	% < 80 ng/ml	Mean ± SD	% < 80 ng/ml	Cotinine (Mean)	% < 80 ng/ml
1	2605,88 ± 1439.30	0	2248,20 ± 1052.47	0	.192	.999
1b[a]	1916,65 ± 922,91	0	1736,81 ± 877,89	0	.341	.999
2	1745,95 ± 1166.14	0	1415,76 ± 762.02	0	.129	.999
2b[a]	1234,22 ± 902.06	2.1	900,21 ± 632. 56	4.4	.046	.969
3	1272,31 ± 831.53	6.4	801,24 ± 567.40	11.1	.003	.664
3b[a]	855,07 ± 655.80	6.4	535,83 ± 408.32	17.8	.007	.173
4	798,61 ± 663.43	8.5	538,39 ± 533.04	17.8	.048	.313
4b[a]	676,39 ± 653.25	14.9	430,95 ±432.04	22.2	.039	.524
5	566,95 ± 883.07	36.2	218,78 ± 378.58	57.8	.023	.038
5b[a]	341,26 ± 718.19	53.2	195,55 ± 372.99	66.7	.235	.269
6	439,72 ± 750.39	53.2	154,44 ± 330.60	71.7	.030	.120
6b[a]	279,94 ± 654.66	63.8	135,93 ± 325.68	73.3	.206	.449
7	281,63 ± 539.04	57.4	159,23 ± 520,71	73.3	.302	.167
7b[a]	260,12 ± 620. 52	70.2	151,67 ± 389.02	68.9	.335	.999

Note. [a] = midweek sessions; % < 80 ng/ml = percentage of participants whose cotinine levels were < 80 nanograms/milliliter.

3.2.Effects of treatment condition on cigarette demand over time

There was no significant effect of treatment condition on cigarette demand (Model D: all p values ≤ .32), suggesting that the differential effect of the CM component was not significant. The group x time interaction was not significant for any cigarette demand index, with the exception of intensity (Model D: $\beta_{4intensity}$ = -0.32, p = 0.004). As shown in Figure 1, as time passes, the intervention that includes CM significantly reduces the intensity index when compared to the intervention that does not include such a component. Although not significant, this trend can be observed for the remaining demand indices (see β_4 in Model D).

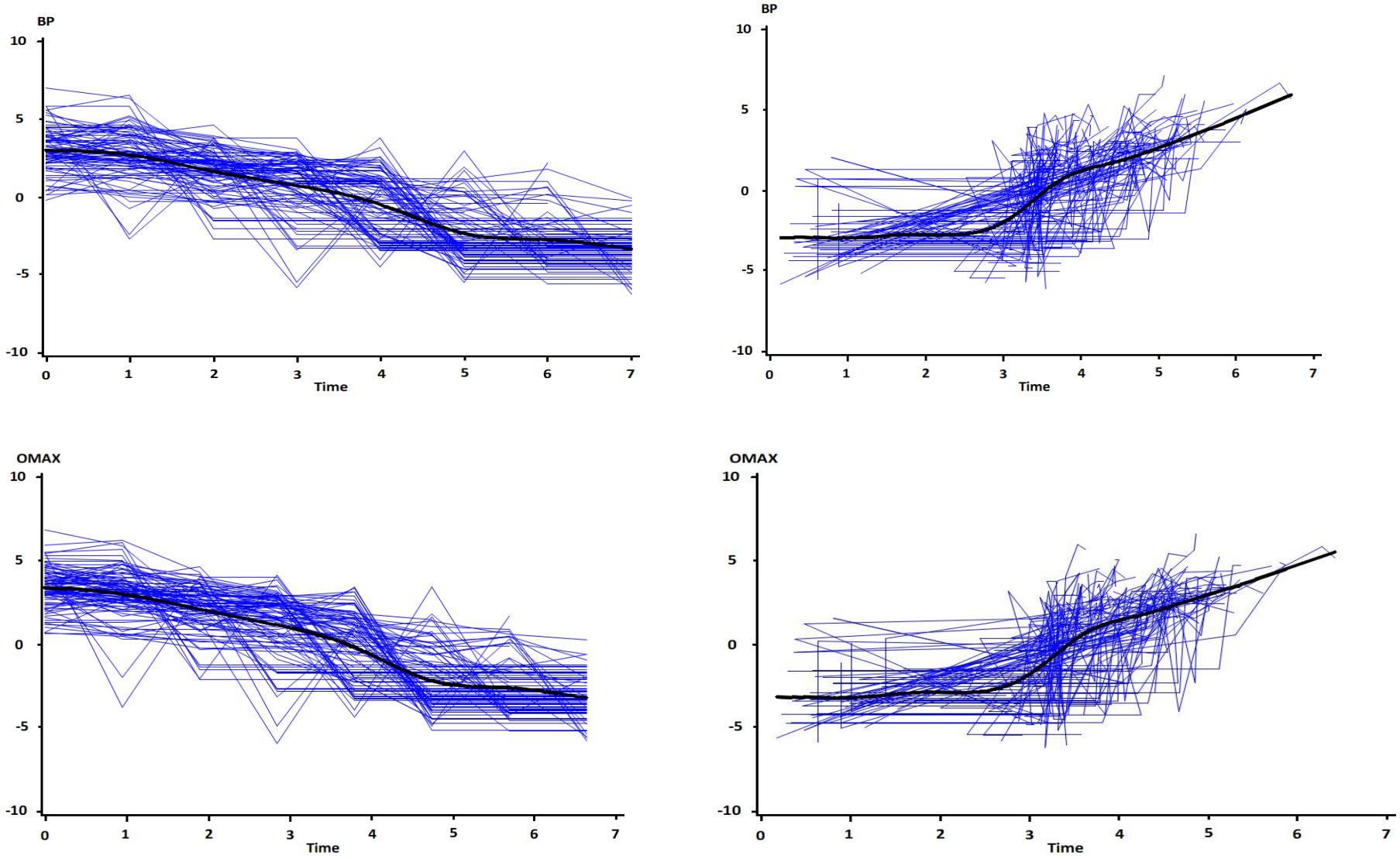
Figure 1 Effect of the group x time interaction on intensity of demand (plotted in logarithmic units.)

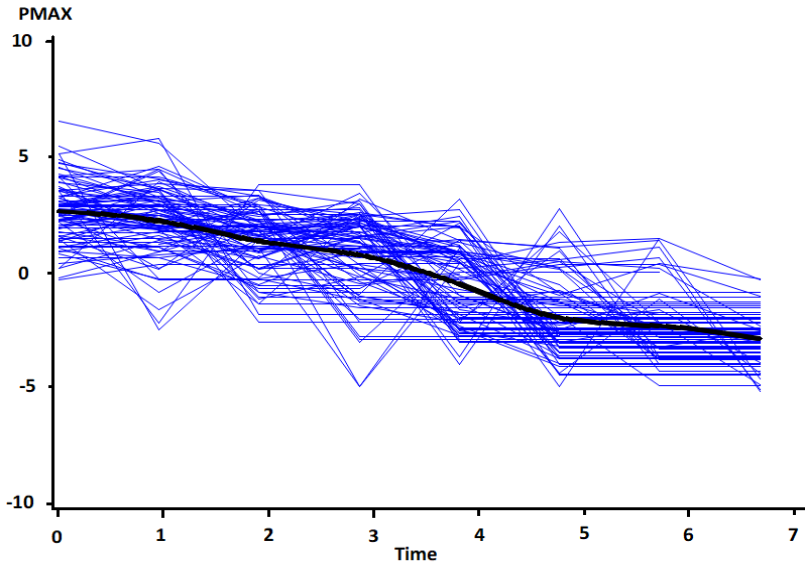


3.3.Effects of smoking consumption in cigarette demand over time

Figure 2 shows changes over time for each CPT index (left panel) as well as cigarette demand modifications plotted by cotinine levels (right panel). In order to differentiate between the cross-sectional and longitudinal effects of cotinine over cigarette demand, both the baseline and actual cotinine values were entered in the model. The association between each CPT index and cotinine level was almost linear (see right panel).

Figure 2 In-treatment changes for each CPT index across sessions (left panel) and association between cigarette demand indices and cotinine levels (right panel). Both CPT indices and cotinine levels are plotted in logarithmic units.

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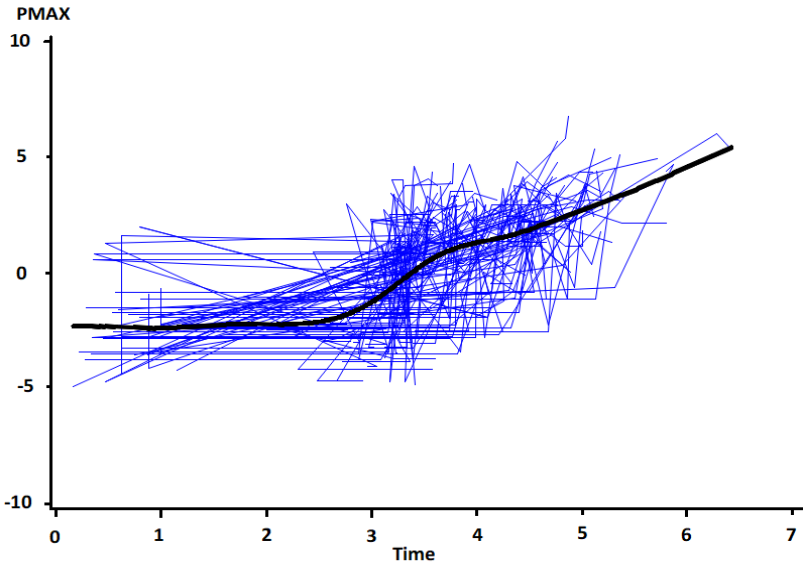
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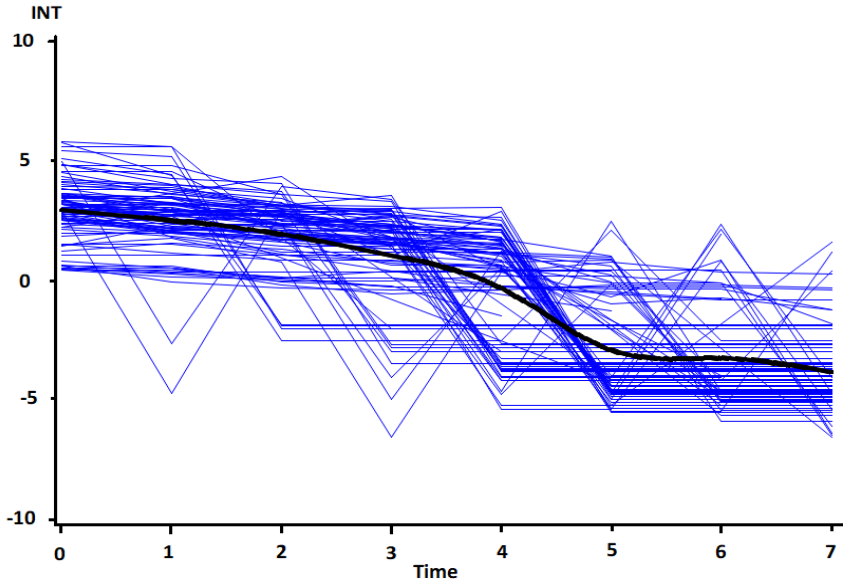
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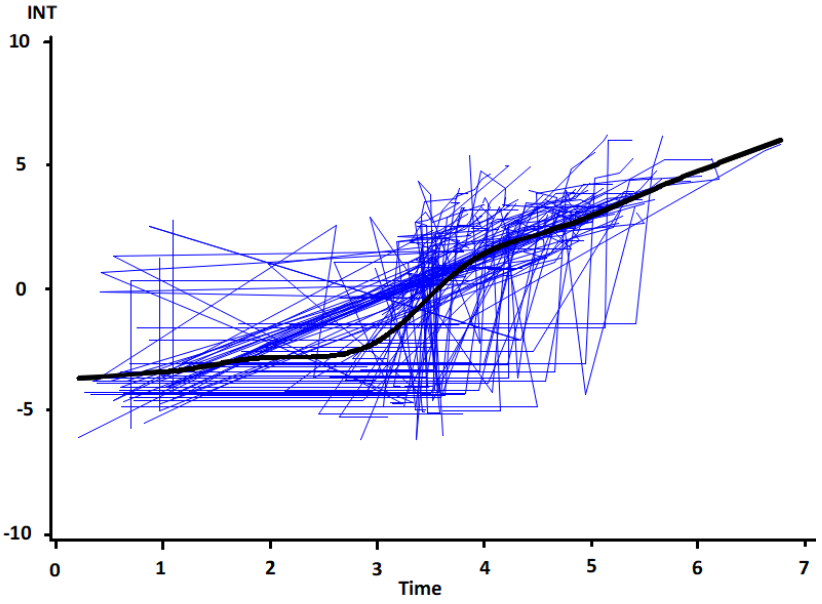
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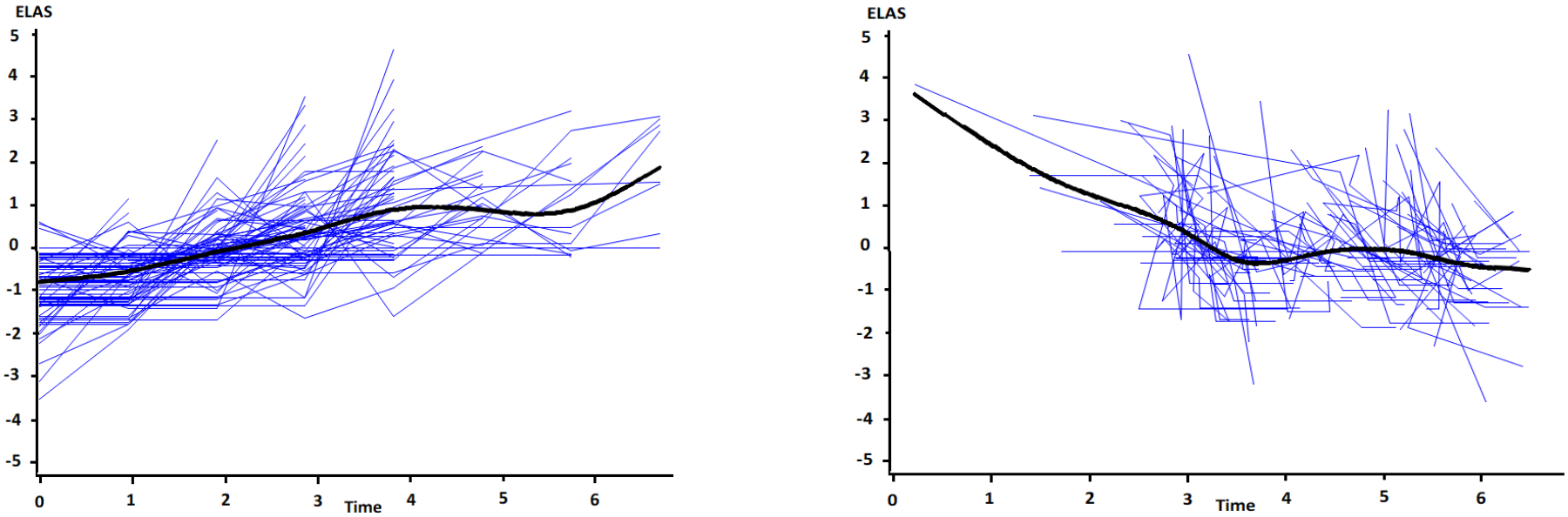

Note. From top to bottom, demand indices are plotted as follows: BP = Breakpoint; Omax; Pmax; Int = Intensity; Elas = Elasticity.

Tables 3-7 show MRM outcomes for each CPT index. Model A includes time (β_3) as the only predictor. Model B adds both baseline (β_1) and actual (β_5) cotinine values. Model C removes baseline cotinine values and incorporates the time x cotinine interaction (β_7). Model D adds group (β_2) and the group x time (β_4) and group x cotinine (β_6) interactions. Results show that cotinine levels were significantly associated with cigarette demand (breakpoint, Pmax, Omax and intensity) over time (see Model C or D in this regard, as both show similar data fit). Specifically, cotinine levels had a significant main effect (Model C: $\beta_{5breakpoint} = 0.57$, $p < 0.001$; $\beta_{5Omax} = 0.54$, $p < 0.001$; $\beta_{5Pmax} = 0.48$, $p < 0.001$; $\beta_{5intensity} = 0.56$, $p < 0.001$). The time x cotinine interaction was also significant (Model C: $\beta_{7breakpoint} = -0.08$, $p < 0.001$; $\beta_{7Omax} = -0.07$, $p < 0.001$; $\beta_{7Pmax} = -0.07$, $p < 0.001$; $\beta_{7intensity} = -0.06$, $p < 0.001$). These results suggest that higher cotinine values are related to higher cigarette demand. The negative time x cotinine interaction suggests that the association between cotinine levels and cigarette demand becomes less prominent as time passes. For instance, for each unit of change in cotinine levels in the first in-treatment session (first week), the breakpoint index increases 0.57 units, while it only increases 0.15 units in the last in-treatment session (seventh week). Elasticity was the only demand index that was not significantly associated with cotinine (see Table 7).

Table 3 Mixed effects regression model with Breakpoint data

	Model A		Model B		Model C		Model D	
Fixed Effect	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept (β_0)	0.78***	0.21	-0.38	2.24	1.14***	0.22	0.99***	0.28
BL (β_1)			0.11	0.29				
Group (β_2)							0.31	0.38
Time (β_3)	-1.08***	0.04	-0.86***	0.06	-1.02***	0.06	-1.01***	0.08
Group×Time (β_4)							-0.01	0.11
Cotinine (β_5)		0.03	0.16***	0.03	0.57***	0.07	0.59***	0.08
Group × Cotinine (β_6)							-0.02	0.05
Time × Cotinine (β_7)					-0.08***	0.01	-0.08***	0.01
Cov Parm	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	1.49***	0.38	0.97**	0.32	0.85**	0.29	0.84**	0.29
Slope	0.03*	0.15	0.04**	0.01	0.04**	0.01	0.04**	0.01
Residual	3.26***	0.21	3.10***	0.21	2.89***	0.19	2.90***	0.19
Goodness-of-fit								
Deviance/AIC/Parms	2585.7/2591.7/6		2450.8/2456.8/8		2437.6/2443.6/8		2444.7/2452.7/11	

Note: AIC: Akaike information criterion; Parms: number of parameters.
*p < .05; **p < .01; ***p < .001

Table 4 Mixed effects regression model for O_{MAX} data

	Model A		Model B		Model C		Model D	
Fixed Effect	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept (β_0)	0.87**	0.20	1.23	1.98	1.19***	0.24	1.02***	0.23
BL (β_1)			-0.08	0.25				
Group (β_2)							0.31	0.36
Time (β_3)	-1.13**	0.04	-0.91***	0.05	-1.06***	0.06	-1.08***	0.08
Group×Time (β_4)							-0.07	0.11
Cotinine (β_5)			0.16***	0.03	0.54***	0.07	0.55***	0.08
Group × Cotinine (β_6)							-0.01	0.05
Time × Cotinine (β_7)					-0.07***	0.01	-0.07***	0.01
Cov Parm	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	0.97***	0.29	0.61**	0.26	0.53*	0.21	0.49*	0.23
Slope	0.02	0.01	0.03*	0.12	0.03**	0.01	0.03*	0.01
Residual	3.41***	0.22	3.21***	0.21	3.03***	0.20	3.05***	0.20
Goodness-of-fit								
Deviance/AIC/Parms	2566.2/2572.2/6		2450.1/2456.1/8		2425.2/2431.2/8		2428.1/2434.1/11	

Note: AIC: Akaike information criterion; Parms: number of parameters.
*p < .05; **p < .01; ***p < .001

Table 5 Mixed effects regression model for P_{MAX} data

	Model A		Model B		Model C		Model D	
Fixed Effect	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept (β_0)	0.58**	0.19	-0.39	2.14	0.86***	0.26	0.76*	0.26
BL (β_1)			0.09	0.28				
Group (β_2)							0.23	0.35
Time (β_3)	-0.91***	0.04	-0.729***	0.05	-0.87***	0.06	-0.84***	0.07
Group×Time (β_4)							-0.05	0.10
Cotinine (β_5)			0.133***	0.02	0.48***	0.07	0.50***	0.07
Group × Cotinine (β_6)							-0.03	0.05
Time × Cotinine (β_7)					-0.07***	0.01	-0.07***	0.01
Cov Parm	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	1.41***	0.34	0.91***	0.28	0.77**	0.26	0.76**	0.28
Slope	0.03*	0.01	0.04**	0.01	0.04**	0.01	0.04**	0.01
Residual	2.66***	0.17	2.56***	0.17	2.42***	0.16	2.42***	0.17
Goodness-of-fit								
Deviance/AIC/Parms	2479.0/2485.0/7		2371.3/2377.3/8		2345.3/2351.3/8		2352.9/2358.9/11	

Note: AIC: Akaike information criterion; Parms: number of parameters.
*p < .05; **p < .01; ***p < .001

Table 6 Mixed effects regression model for Intensity data

	Model A		Model B		Model C		Model D	
Fixed Effect	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept (β_0)	1.17*	0.19	-1.38	1.95	1.28***	0.24	1.41***	0.30
BL (β_1)			0.03	0.25				
Group (β_2)							-0.40	0.41
Time (β_3)	-1.20***	0.05	-0.88***	0.06	-0.99***	0.06	-1.12***	0.08
Group×Time (β_4)							-0.32**	0.11
Cotinine (β_5)			0.24***	0.03	0.56***	0.08	0.49***	0.09
Group × Cotinine (β_6)							0.09	0.05
Time × Cotinine (β_7)					-0.06***	0.01	-0.05***	0.01
Cov Parm	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	0.81***	0.22	0.80***	0.22	0.82**	0.22	0.70***	0.20
Residual	4.01***	0.26	4.01***	0.26	3.88***	0.25	3.87***	0.25
Goodness-of-fit								
Deviance/AIC/Parms	2708.7/2712.7/4		2552.3/2556.3/6		2541.4/2545.4/6		2537.5/2541.5/9	

Note: AIC: Akaike information criterion; Parms: number of parameters.
*p < .05; **p < .01; ***p < .001

Table 7 Mixed effects regression model for Elasticity data

	Model A		Model B		Model C		Model D	
Fixed Effect	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept (β_0)	-0.35***	0.10	0.30	1.27	-0.30*	0.12	-0.33*	0.16
BL (β_1)			-0.08	0.16				
Group (β_2)							0.07	0.20
Time (β_3)	0.55***	0.05	0.52***	0.06	0.52***	0.06	0.48***	0.08
Group×Time (β_4)							0.08	0.12
Cotinine (β_5)			-0.04	0.04	-0.01	0.11	-0.01	0.13
Group × Cotinine (β_6)							0.01	0.08
Time × Cotinine (β_7)					-0.01	0.02	-0.01	0.02
Cov Parm	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	0.07	0.10	0.05	0.10	0.04	0.10	0.04	0.10
Slope	0.12***	0.03	0.13***	0.03	0.13***	0.03	0.13***	0.03
Residual	0.61***	0.06	0.62***	0.06	0.63***	0.06	0.63***	0.06
Goodness-of-fit								
Deviance/AIC/Parms	1017.1/1023.1/6		989.9/995.9/8		994.2/1000.2/8		1000.2/10006/11	

Note: AIC: Akaike information criterion; Parms: number of parameters.
Note: *p < .05; **p < .01; ***p < .001

4. Discussion

The aims of this study were to assess the differential effect of treatment condition (CBT + BA versus CBT + BA + CM) on cigarette demand, and to explore whether changes in smoking intake evidenced by cotinine levels affect in-treatment cigarette demand. The main findings are the following: 1) participants receiving CBT + BA + CM showed higher reductions in cigarette demand across sessions when compared to participants in CBT + BA, though this comparison was only significant for intensity of demand; 2) cotinine levels were positively associated with cigarette demand indices; 3) the relationship between cotinine levels and cigarette demand was stronger during the first sessions, when smoking consumption was still high, and becomes less pronounced across sessions; and 4) In-treatment decreases in cotinine levels were associated with reductions in cigarette demand over time, although this association did not reach significance for the elasticity index.

The results herein indicated that the additive effect of CM over a depression-focused BA treatment reduces intensity of demand through the course of treatment. Two rationales might account for this result. First, it may be that the expectation of receiving vouchers upon abstinence is promoting patients' adherence to weekly nicotine intake reductions early in treatment, thereby lessening the relative reinforcing efficacy of nicotine. In the present study, larger cotinine reductions were obtained for the CM group in the majority of the sessions (weeks 2-6), probably reflecting a greater reduction of volumetric self-reported consumption. It might also be possible that the CM escalating magnitude of reinforcement is operating in this result. As occurs in weeks 5-6, the voucher´s value itself seems to increase the cost opportunity of smoking and thus motivate individuals to reduce their tobacco consumption. However, the fact that groups did not differ in their cotinine levels in sessions 6b and 7a-7b evidences the need to intensify the reinforcing magnitude in order to promote patients' abstinence.

The present research shows that nicotine consumption assessed by cotinine levels is positively related to cigarette demand. This finding aligns with previous research showing greater cigarette demand in heavy smokers compared to light smokers (Higgins et al., 2017). The present result adds further evidence of the convergent validity of the CPT by demonstrating that cigarette demand is reflected in naturalistic smoking variables such as cigarette consumption (MacKillop et al., 2008). Moreover, highly reliable smoking biomarkers such as urine cotinine have been scarcely used in previous studies addressing cigarette demand (Bidwell, MacKillop, Murphy, Tidey, & Colby, 2012), so the fact the present study assesses it, provides solid support for the validity of cigarette demand measures.

In accordance with behavioral economic research showing that the effect of increasing the cost of a given reinforcer is dependent on the location of the demand curve (Green & Kagel, 1996), an interesting and novel finding is that the association between cotinine levels and cigarette demand is stronger during the first sessions (that is, when smoking consumption is still high), but declines as the end of treatment approaches (when smoking intake has been significantly reduced). As recent evidence shows that cigarette demand is potentially variable in response to tax rises (Grace et al., 2015a; Grace, Kivell, & Laugesen, 2015b), an important implication derived from the present study is that changes in tobacco price would have a stronger impact on heavy smokers than light smokers. The present result is interesting since there are important gaps regarding the influence of cigarette price on special populations such as heavy and/or long-term smokers (Bader, Boisclair, & Ferrence, 2011). This evidences the need for further research on this topic.

Lastly, reductions in cotinine levels were associated with rapid decreases in cigarette demand over an 8-week treatment program. This result shows a clear correspondence with the recent experimental study from Smith et al. (2017), who found that participants smoking cigarettes with low nicotine content during a 6 week period decreased the majority of the demand parameters (intensity, elasticity, Pmax and Omax) for study cigarettes when compared to the control group. As in the Smith et al. (2017) study, we did not find statistically significant changes in elasticity; this was probably due to the fact that, as the intervention went on, the proportion of participants who reported that they would not smoke at all prices (including \$0.00 or all prices > \$0.00) increased considerably. For instance, demand data from 65.2% participants could be used for obtaining elasticity in the fourth in-treatment session, while this percentage dropped to 8.7% in the last in-treatment session (seventh week). Hence, those

participants whose cotinine levels show the strongest reduction were not included in the elasticity analyses, reducing the statistical power to detect significant decreases in this demand index.

Several limitations of the study merit mention. First, cigarette demand was assessed using a hypothetical cigarette purchase task. Nevertheless, with the exception of lower elasticity of demand found in the hypothetical CPT version, previous research indicates no systematic differences between performance on hypothetical and actual purchase tasks (Wilson et al., 2016). Second, although the sample size was adequate for studies of drug demand, it is probable that a bigger one would transform the reduction tendency observed in some of the analyses into a statistically significant decrease. Lastly, the study was conducted with smokers with elevated depressive symptoms, precluding these findings from being generalizable to smokers with minimal depression or smokers who are not depressed.

Even with these limitations, the present study suggests that cigarette demand is mainly a state variable and that reductions in nicotine consumption arranged over the course of the treatment decrease the reinforcing value of smoking. Thus, nicotine fading should be considered as an effective strategy by policy makers and health professionals responsible for designing smoking cessation interventions.

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References

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders* (4th revised ed.). Washington, DC: American Psychiatric Association.

Bader, P., Boisclair, D., & Ferrence, R. (2011). Effects of tobacco taxation and pricing on smoking behavior in high risk populations: a knowledge synthesis. *International Journal of Environmental Research and Public Health, 8*, 4118-4139. doi: 10.3390/ijerph8114118

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for Beck Depression Invertory-II*. San Antonio, TX: Psychological Corporation.

Bidwell, L. C., MacKillop, J., Murphy, J. G., Tidey, J. W., & Colby, S. M. (2012). Latent factor structure of a behavioral economic cigarette demand curve in adolescent smokers. *Addictive Behaviors, 37*, 1257-1263. doi: 10.1016/j.addbeh.2012.06.009

Connor Gorber, S., Schofield-Hurwitz, S., Hardt, J., Levasseur, G., & Tremblay, M. (2009). The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. *Nicotine & Tobacco Research, 11*, 12-24. doi: 10.1093/ntr/ntn010

Chase, H. W., MacKillop, J., & Hogarth, L. (2013). Isolating behavioural economic indices of demand in relation to nicotine dependence. *Psychopharmacology, 226*, 371-380. doi: 10.1007/s00213-012-2911-x

Few, L. R., Acker, J., Murphy, C., & MacKillop, J. (2012). Temporal stability of a Cigarette Purchase Task. *Nicotine & Tobacco Research, 14*, 761-765. doi: 10.1093/ntr/ntr222

First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J. B. W. (1996). *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV).* Washingyon, D.C: American Psychiatric Press, Inc.

Grace, R. C., Kivell, B. M., & Laugesen, M. (2015a). Assessing the temporal stability of a Cigarette Purchase Task after an excise tax increase for factory-made and roll-your-own smokers. *Nicotine & Tobacco Research, 17*, 1393-1396. doi: 10.1093/ntr/ntv025

Grace, R. C., Kivell, B. M., & Laugesen, M. (2015b). Predicting decreases in smoking with a cigarette purchase task: evidence from an excise tax rise in New Zealand. *Tobacco Control, 24*, 582-587. doi: 10.1136/tobaccocontrol-2014-051594

Green, L., & Kagel, J. H. (1996). *Advances in behavioral economics: substance use and abuse* (Vol. 3). Norwood, NJ: Ablex Publishing Corporation.

Hasin, D. S., O'Brien, C. P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., . . . Grant, B. F. (2013). DSM-5 criteria for substance use disorders: Recommendations and rationale. *The American journal of psychiatry, 170*, 834-851. doi: 10.1176/appi.ajp.2013.12060782

Heatherton, 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. doi: 10.1111/j.1360-0443.1991.tb01879.x

Higgins, S. T., Reed, D. D., Redner, R., Skelly, J. M., Zvorsky, I. A., & Kurti, A. N. (2017). Simulating demand for cigarettes among pregnant women: A low-risk method for studying vulnerable populations. *Journal of the Experimental Analysis of Behavior, 107*, 176-190. doi: 10.1002/jeab.232

Hursh, S. R., & Roma, P. G. (2013). Behavioral economics and empirical public policy. *Journal of the Experimental Analysis of Behavior, 99*, 98-124. doi: 10.1002/jeab.7

Hursh, S. R., & Silberberg, A. (2008). Economic demand and essential value. *Psychological Review, 115*, 186-198. doi: 10.1037/0033-295x115.1.186

Koffarnus, M. N., Franck, C. T., Stein, J. S., & Bickel, W. K. (2015). A modified exponential behavioral economic demand model to better describe consumption data. *Experimental and Clinical Psychopharmacology, 23*, 504-512. doi: 10.1037/pha0000045

Mackillop, J., Murphy, C. M., Martin, R. A., Stojek, M. , Tidey, J. W., Colby, S. M., & Rohsenow, D. J. (2016). Predictive validity of a Cigarette Purchase Task in a randomized controlled trial of contingent vouchers for smoking in individuals with substance use disorders. *Nicotine & Tobacco Research, 18*, 531-537. doi: 10.1093/ntr/ntv233

MacKillop, J., Murphy, J. G., Ray, L. A., Eisenberg, D. T. A., Lisman, S. A., Lum, J. K., & Wilson, D. S. (2008). Further validation of a cigarette purchase task for assessing the relative reinforcing efficacy of nicotine in college smokers. *Experimental and Clinical Psychopharmacology, 16*, 57-65. doi: 10.1037/1064-1297.16.1.57

MacPherson, L., Collado, A, Lejuez, C. W., Brown, R. A., & Tull, M. T. (2016). Behavioral activation treatment for smoking (BATS) in smokers with depressive symptomatology. *Advances in Dual Diagnosis, 9*, 85-96. doi: 10.1108/ADD-02-2016-0005

Murphy, C. M., MacKillop, J., Martin, R. A., Tidey, J. W., Colby, S. M., & Rohsenow, D. J. (2017). Effects of varenicline versus transdermal nicotine replacement

therapy on cigarette demand on quit day in individuals with substance use disorders. *Psychopharmacology (Berl), 234*, 2443-2452. doi: 10.1007/s00213-017-4635-4

Schlienz, N. J., Hawk, L. W. Jr., Tiffany, S. T., O'Connor, R. J., & Mahoney, M. C. (2014). The impact of pre-cessation varenicline on behavioral economic indices of smoking reinforcement. *Addictive Behaviors, 39*, 1484-1490. doi: 10.1016/j.addbeh.2014.05.008

Secades-Villa, R., García-Rodríguez, O., López-Núñez, C. , Alonso-Pérez, F., & Fernández-Hermida, J. (2014). Contingency management for smoking cessation among treatment-seeking patients in a community setting. *Drug and Alcohol Dependence, 140*, 63-68. doi: 10.1016/j.drugalcdep.2014.03.030

Secades-Villa, R., Pericot-Valverde, I., & Weidberg, S. (2016). Relative reinforcing efficacy of cigarettes as a predictor of smoking abstinence among treatment-seeking smokers. *Psychopharmacology (Berl), 233*, 3103-3112. doi: 10.1007/s00213-016-4350-6

Secades-Villa, R., Weidberg, S., Gonzalez-Roz, A., Reed, D. D., & Fernandez-Hermida, J. R. (2017). Cigarette demand among smokers with elevated depressive symptoms: an experimental comparison with low depressive symptoms. *Psychopharmacology (Berl)*. Advance online publication. doi: 10.1007/s00213-017-4788-1

Singer, J. D. , & Willett, J. B. (2003). *Applied longitudinal data analysis: Modeling change and event ocurrence.* New York, NY: Oxford University Press.

Smith, T. T., Cassidy, R. N., Tidey, J. W., Luo, X., Le, C. T., Hatsukami, D. K., & Donny, E. C. (2017). Impact of smoking reduced nicotine content cigarettes on

sensitivity to cigarette price: further results from a multi-site clinical trial. *Addiction, 112,* 349-359. doi: 10.1111/add.13636

Tabachnick, B. G, & Fidell, L. S. (2006) (2006). *Using multivariate statistics (5th ed.).* Needham Heights, MA: Allyn & Bacon, Inc.

Vallejo, G., Fernández, M. P., Livacic-Rojas, P. E., & Tuero-Herrero, E. (2011). Comparison of modern methods for analyzing unbalanced repeated measures data with missing values. *Multivariate Behavioral Research, 46,* 900-937. doi: 10.1080/00273171.2011.625320

Wilson, A. G., Franck, C. T., Koffarnus, M. N., & Bickel, W. K. (2016). Behavioral economics of Cigarette Purchase Tasks: Within-subject comparison of real, potentially real, and hypothetical cigarettes. *Nicotine & Tobacco Research, 18,* 524-530. doi: 10.1093/ntr/ntv154

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Conflict of interest:

None

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