**High Dose Bupropion Treatment for Smoking Cessation**
**NCT Number not yet assigned**
**Date of Document: 8/25/2017**

## SPECIFIC AIMS

Smokers with psychiatric symptoms and conditions (SWPS) struggle to quit and account for a mounting proportion of the U.S. tobacco-related disease burden each year.[1] This population has high relapse rates, even when receiving front-line treatments[2] and specialized interventions (e.g., mood management cessation counseling).[3] The multitude of different types of psychiatric symptoms that co-occur with smoking further compounds this problem and many SWPS experience symptoms of 2+ conditions (e.g., depression + PTSD).[4]

To address this complex problem, we have departed from the traditional approach of segmenting the population of SWPS by syndrome. Instead, we have investigated cross-cutting (transdiagnostic) psychiatric vulnerabilities implicated in the etiology of numerous psychopathologies as determinants of relapse risk in the diagnostically-heterogeneous population of SWPS. Anhedonia—diminished happiness, interest, and pleasure from normally-enjoyable experiences—is one such vulnerability that is fairly common (i.e., estimated 43% of smokers experience significant anhedonia at some point in their lifetime) may underlie the comorbidity of smoking with numerous psychiatric syndromes.[4] In the prior funding period, we executed laboratory-based research of mechanisms underlying relapse in anhedonic smokers to inform targets for treatment. We found that anhedonia-related deficits in reward processing that are believed to stem from hypodopaminergic striatal pathophysiology[5] are: (1) temporarily offset by nicotine,[6] and (2) unmasked and exacerbated in withdrawal, causing profound deficiencies in positive mood,[7] increases in urge to smoke for pleasure,[8] and heightened propensity to relapse to remediate these deficits.[9] This continuation application leverages and translates our laboratory results into the treatment development arena to improve upon the standard of care for SWPS.

Bupropion is an anti-depressant that increases striatal dopamine transmission,[10] improves reward processing[10] and is widely available at a modest cost.[11] The standard 300 mg/day dose of bupropion has demonstrated clear efficacy for smoking cessation in various populations.[12,13] Outside of the smoking literature, high dose bupropion (400-450 mg/day) exhibits superior efficacy relative to the 300 mg/day dose for treating psychiatric disorders,[14,15] reducing weight and body fat,[16] and alleviating anhedonia,[14] without meaningfully increasing side effects.[17] Thus, high dose bupropion may be particularly effective at promoting smoking cessation in anhedonic smokers, improving anhedonia-related mental health, and preventing post-quit weight gain. To the best of our knowledge, 300 mg/day is the highest bupropion dose tested for smoking cessation in any population to date.

In this continuation proposal, we translate work in the prior period on mechanisms underlying relapse in anhedonic smokers to the development of a novel, disseminable, and putatively effective treatment for this high risk population. We propose a clinical trial in which anhedonic smokers are provided standard cessation counseling and randomized to either: the standard 300 mg/day dose of bupropion (BUP-300; N=150) or a high 450 mg/day dose (BUP-450; N=150). In addition to treatment effects on 7-day point prevalence smoking abstinence (PPA) outcomes, we will: i) examine if improvement in reward processing is a mechanism of action for BUP-450's efficacy with innovative laboratory-based computer task and subjective indices of reward processing, ii) assess moderators of treatment efficacy, iii) investigate treatment effects on secondary mental health and body weight and adiposity outcomes; and iv) utilize the extended release (XL) formulation that requires dosing only once per day, which has yet to be tested for cessation and may increase adherence.

### Primary Aims

1. **To test the efficacy of high dose bupropion for smoking cessation in anhedonic smokers.** Hyp 1. PPA rates across the 6-month post-quit follow-up period will be higher in BUP-450 vs. BUP-300.
2. **To test whether treatment-related enhancement of reward processing is a mechanism of action of high dose bupropion**. Hyp 2. The effects of BUP-450 vs. BUP-300 cessation outcomes will be mediated by reward processing, such that dose will predict greater improvements in reward processing, which will in turn be associated with greater odds of abstinence.

### Secondary Aims

3. **To test the effects of high dose bupropion on secondary outcomes of:** (a) anhedonia and related psychopathology (i.e., depressive, social anxiety, ADHD, PTSD symptoms), and (b) change in body weight and percent body fat composition.
4. **To examine if baseline anhedonia level and related psychopathology (depressive, social anxiety, ADHD, PTSD symptoms) moderate the efficacy of high dose bupropion on cessation outcome**.

If successful, this research may identify a novel, highly-disseminable, cost-effective, and efficacious cessation treatment for an at-risk population, with wide-spanning implications toward offsetting three of the nation's top causes of morbidity and mortality—smoking, mental illness, and health problems due to excessive weight.

## A. SIGNIFICANCE

### A.1 Importance of Increasing Cessation Treatment Outcomes for Smokers Psychiatric Symptoms

While the overall population-level rate of smoking has significantly declined in recent years, smoking among those with psychiatric symptoms and conditions has remained stable,[18] with SWPS accounting for a mounting proportion of the U.S. tobacco-related disease burden each year.[1] A key source of the tobacco-related health disparities facing SWPS is their disproportionately low quit rates.[1] Hence, improving smoking cessation among SPWS is vital for reducing tobacco-related disparities and counteracting the public health burden of smoking.

### A.2 Current Status of Cessation Treatment Development Research for SWPS

The predominant approach in smoking cessation research for SWPS has been to segment smokers based on psychiatric syndrome and test treatments in diagnostically-homogenous samples (e.g., smokers with DSM-IV PTSD,[19] major depressive disorder,[20] elevated score on a symptom composite index).[21] With this approach, advancement of clinical science and care for SWPS has been modest. In some cases, smokers with a particular syndrome have failed to respond to an active (vs. inactive) treatment[22] or have responded more poorly than those without psychiatric problem.[23,24] In one circumstance, a specialized intervention for smokers with a specific comorbid syndrome produced poorer mood than standard counseling (e.g., CBT for depression-integrated cessation counseling for depressed smokers).[25] Often the best case scenario is that a treatment is efficacious amongst smokers with a psychiatric syndrome (e.g., bupropion, varenicline, nicotine replacement, nortriptyline);[22,26] yet, it fails to offset the disparity in quit success by psychiatric status.[27] That is, despite a medication successfully improving outcomes relative to placebo amongst those with a psychiatric syndrome, quit rates after active treatments are still lower in those with (vs. without) a psychiatric syndrome.[26]

### A.3 Why the Impact of Syndrome-Based Approaches to Cessation Research in SWPS Has Been Modest

We believe that the following key clinical and scientific barriers to the standard approach of grouping smokers by syndrome or diagnosis has obstructed progress toward developing more effective treatments for SWPS.

**Syndrome approaches fail to address the substantive heterogeneity within individual disorders**. Many disorders have multiple well-defined empirically-distinct symptom subtypes or factors (e.g., negative affect vs. somatic features in depression, re-experiencing vs. numbing in PTSD) with unique etiological correlates.[28] Such heterogeneity suggests that there are multiple, distinct etiologic underpinnings of a single syndrome.[29] Hence, individuals who share the same psychiatric diagnosis may have distinct symptoms, unique psychiatric influences on their smoking, and therefore benefit from different smoking intervention approaches.[30]

**Syndrome approaches do not address the co- and multi-morbidity across multiple disorders**. The extensive comorbidity among psychiatric disorders have prompted proposals that different disorders may be 'alternate manifestations' of a common underlying etiology (e.g., internalizing dysfunction).[31] Thus, people with different syndromes may have shared psychopathological influences on their smoking[32] and may benefit from a common clinical strategy. This is a vital conclusion, given that the disproportionate relapse risk among SWPS is pervasive across numerous symptoms and syndromes, including depression, mania, generalized anxiety disorder, social phobia, ADHD, PTSD, borderline personality disorder, psychosis, alcohol and drug use disorder, and others.[4,33,34] Further, many SPWS experience symptoms from 2, 3, or 4+ different disorders.[23] Thus, segregating SWPS by diagnosis and applying disorder-specific interventions may not be maximally effective. The extensive resources required to test disorder-specific approaches, disseminate such information to the clinicians, and recommend that clinicians adopt disorder-specific treatment rules is less than ideal.

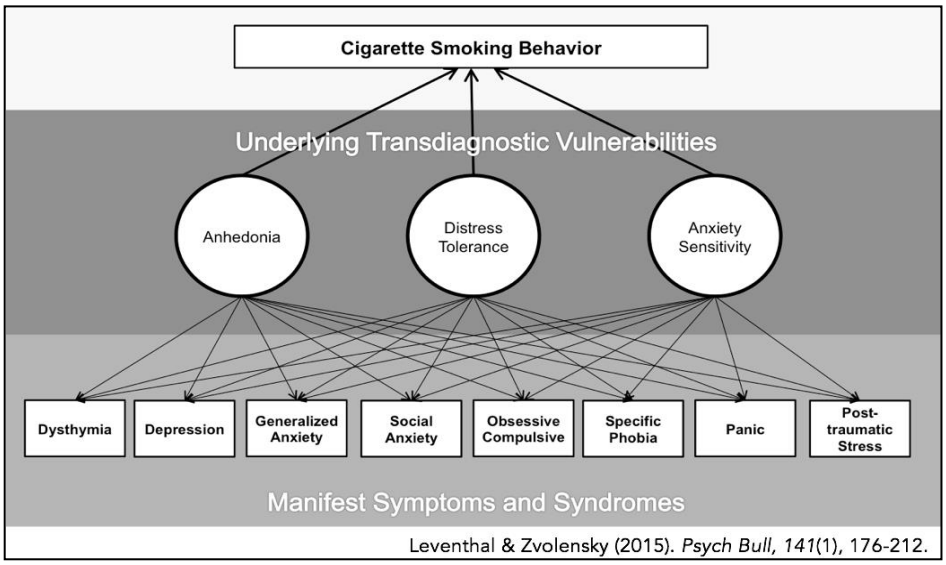
**Syndrome approaches equally weight all symptoms in defining those at risk, but certain symptoms have minimal etiologic effects on smoking.** Analyses at the individual symptom level has not effectively linked several disorder-specific symptoms to difficulty quitting (e.g., hypersomnia in major depression,[35] inattention in ADHD).[36] Thus, grouping smokers together based on diagnostic or syndrome-based scheme may inappropriately include a portion of low-risk SWPS without a psychiatrically-determined vulnerability to relapse.

### A.4 Why A Transdiagnostic Framework to Addressing Cessation in SWPS Could Break New Ground

The NIMH Research Domain Criteria propose that transdiagnostic cross-cutting dimensions, traits, and neural circuits underpin and account for the presentation and co-occurrence of various disorders.[37] Similarly, we have studied trandiagnostic “reactive” vulnerabilities for psychopathology—tendency toward maladaptive responses to emotional stimuli and states (e.g., distress intolerance, negative urgency, anxiety sensitivity) that serve to enhance or diminish the normative reaction to emotion stimuli.[4] Such vulnerabilities result in an excess or defi-

cit, respectively, beyond typical emotional functioning, which in turn increase risk for a variety of psychiatric symptoms disorders.[37] Specific symptomatic expression may be dependent more on external context than heritable disposition (e.g., amongst individuals with the same reactive vulnerability, one may develop social anxiety if ostracized during childhood whereas the other PTSD if exposed to physical abuse).

For SWPS, smoking may represent a manifestation of the maladaptive response to emotion states that characterizes underlying psychiatric vulnerability. People with such vulnerabilities may be hyper-motivated to respond to emotional excesses or deficits with smoking behavior to regulate affect, because they might otherwise not be able to regulate mood using healthy strategies. Consequently, smokers with reactive vulnerabilities may place great salience on the reinforcing value of smoking-induced affect modulation and find quitting particularly difficult. Given this premise, a small set of transdiagnostic vulnerabilities may explain the liability to smoking relapse common to various types of psychopathology (figure). The proposed research applies this framework to one such vulnerability.




## A.5 Anhedonia: A Promising Transdiagnostic Source of Cessation Relapse Risk in SWPS

**Definition.** Resulting from diminished reward functioning, anhedonia clinically presents as deficient happiness and enjoyment as well as decreased pleasure from and interest in non-drug (natural) rewarding stimuli that are commonly rewarding.[4] The diminished hedonic response to and interest in non-drug rewards is posited to be underpinned by attenuated mesolimbic activity and reduced sensitivity to the effects of non-drug rewarding stimuli on phasic mesolimbic dopamine release.[38] Anhedonia is an endophenotype for psychopathology[39] that is expressed in two ways. For some, anhedonia is a state that is acutely elevated in the context of an active psychiatric episode or in response to stress,[40,41] becomes 'dormant' in between episodes, and regularly re-manifests during distress states. For others, anhedonia a trait-like dimension with modest fluctuation across time.[42,43] Though often present in depression, anhedonia is only modestly associated with other depressive symptoms (φs .09-.58).[44] Anhedonia is common with 25% of the US population and 43% of smokers experiencing lifetime anhedonia.[45,46] Anhedonia may give rise to patterns of behavioral and social withdrawal, low motivation for long-term goal attainment, disrupted social development, affective restriction and flattening, fatigue, and other processes that increase risk for various psychopathologies.[4] As a characterizing feature and putative vulnerability for several syndromes (e.g., PTSD,[47] ADHD,[48] bipolar disorder,[49] alcohol/drug use disorder,[50] OCD,[51] borderline personality,[52] psychosis,[53] social anxiety),[54] anhedonia truly is transdiagnostic.

**Evidence of anhedonia as a contributor to smoking persistence and relapse.** Anhedonia is associated with several markers of tobacco addiction (e.g., craving,[55] withdrawal,[56] and dependence).[45,57] Evidence from 7 studies in combined 2,083 smokers show that anhedonia predicts failure to reach abstinence, transitioning from lapse to relapse, shorter latency to (re)lapse, and lower PPA rates.[45,56-60] These associations generalize across smokers receiving minimal treatment (e.g., self-help booklets)[58,59] and intensive treatments (e.g., medication + counseling),[45,56,57] are found using various anhedonia measures (e.g., trait,[59] current state level,[56] lifetime status[45]) and definition (e.g., diminished pleasure,[57,59] interest,[58] enjoyment[56]), and are incremental to control for demographics, cig/day, nicotine dependence, and various symptoms and disorders (e.g., anxiety, substance use, major depressive, and bipolar disorder, recurrent depression, negative affect, sleep/appetite problems). Two studies have not found this association, one of which may have been underpowered (N=87).[61] The other showed that individuals who scored above (vs. below) a cutoff for severe anhedonia at pre-quit had *higher* PPA rates at 8-week follow-up,[62] though changes in a different anhedonia indicator predicted relapse in a separate paper.[62] Though unclear whether the divergence of these two studies from others is systematic or due to error, the preponderance of evidence demonstrates that anhedonia is a robust risk factor for relapse.

## A.6 Mechanisms linking Anhedonia and Smoking Relapse Risk

With the goal of identifying treatment targets, we proposed a model of intermediate mechanisms linking anhedonia and smoking relapse.[4] The model purports that when anhedonic individuals start smoking, pre-existing deficits in their ability to process and respond to natural rewards are alleviated because of nicotine is a reward-enhancer that increases the reinforcing properties of (and phasic dopamine bursts in response to) non-drug rewards.[63-65] The nicotine bolus from each cigarette allows anhedonic smokers to experience temporary moments of pleasure and interest towards natural reward. Yet, when anhedonic smokers quit, pre-existing deficits in reward processing become unmasked and exacerbated by withdrawal-induced hyperdopaminergia, producing profound deficits in pleasure experience that motivate relapse back to smoking to re-attain nicotine-induced reward processing enhancement. Upon lapse, anhedonic smokers may derive greater nicotine reward from the lapse experience, which may in turn promote transition from lapse to relapse.

Empirical support for this model has accumulated in laboratory research supported in this grant's prior funding period (see C.1). Smokers with higher (vs. lower) anhedonia exhibit greater: (a) mood enhancement in response to natural rewards when given nicotine,[66] (b) abstinence-induced deficits in pleasure, positive mood, processing of reward-related stimuli;[6,7,55] and (c) abstinence-induced increases in urge to smoke for pleasure.[8] The association of anheonida with lapse behavior is mediated by deficient positive mood.[9] Thus, quit success among anhedonic smokers could be improved by treatments that ameliorate hypodopaminergia, improve reward processing, enhance positive mood, diminish urge, and block nicotine reward derived from smoking.

## A.7 Rationale for Choosing Bupropion to Treat Anhedonic Smokers

**Bupropion targets the mechanisms underlying anhedonia's influence on relapse**. Bupropion has demonstrable effects on boosts in positive mood, pleasure, cognitive processing of reward-related stimuli, and attenuation of smoking urge and behavioral signs of anhedonia during nicotine withdrawal.[14,67,68] These effects appear to be mediated by bupropion's dopamine reuptake inhibition which enhances tonic and phasic striatal dopamine release.[68] Bupropion a nicotine acetylcholine receptor antagonist as well, and translational studies indicate bupropion's ability to block the rewarding effects of nicotine in animals and in humans,[69-71] Fatigue and amotivation, which co-occur with anhedonia, are improved by bupropion norepinephrine reuptake inhibition.[72]

**Bupropion is highly disseminable and efficacious.** Bupropion at 300mg/day (BUP-300) is efficacious, safe, and tolerable.[72] As one of the most widely prescribed medications in the US,[73] clinicians are often comfortable prescribing bupropion to a wide range of patients because it is available in a generic at a fairly low cost and has FDA approved indications for smoking, depression, and (in combination with naltrexone) obesity. Hence, new evidence supporting a novel application of bupropion would be readily adopted by the clinical community.

**Specialized behavioral treatments have not been successful.** We developed positive psychotherapy for smoking cessation—a novel intervention aimed to ameliorate pleasure by teaching skills to obtain pleasure through healthy means without resorting to smoking via several exercises (e.g., savoring pleasant experiences by being mindful and cultivating and prolonging the positive mood).[74] A pilot RCT showed that while it outperformed standard treatment in the overall sample, positive psychotherapy for smoking cessation did not improve quit outcomes relative to standard cessation counseling amongst anhedonic smokers.[74] Another treatment that promotes the identification of and engagement in pleasant activities—behavioral activation for smoking cessation—showed evidence of efficacy in a RCT, but did not affect anhedonia.[75] We suspect that because anhedonia is stable and heritable neurobehavioral phenotype,[76] pharmacological aids that correct underlying neurocircuitry may have a greater chance or producing a faster and more robust clinical response.

**Other pharmacological treatments may be less favorable.** While nicotine is an acute reward enhancer,[77] pre-quit anhedonia predicts worse cessation outcomes in smokers treated with nicotine replacement (NRT).[56] We presume that the slower speed of nicotine absorption of NRT (in comparison to cigarettes) may not produce a enough of a robust and sustained effect to entirely reverse anhedonia-related reward processing deficits, leaving remaining disparities in quit outcomes for anhedonic smokers. Bupropion treatment for 3+ weeks produces an anti-depressant effect that may treat the underlying deficiency.[78] Varenicline is another option, although it may not impact anhedonia-related pathology.[79] Further, despite recent evidence that varenicline does not produce significant psychiatric side effects,[13] prior FDA black box contraindications for psychopathology may still leave some clinicians hesitant to prescribe varenicline for SWPS.

## A.8 High Dose Bupropion is Yet to be Tested for Cessation and may be Highly Effective for Anhedonics

Buproion's standard dose is 300 mg/day, which clearly improves outcomes relative to PLA, but does not regularly outperform nicotine replacement and is generally less efficacious than varenicline.[26] BUP-300 could be

insufficient for maximizing clinical effects because relative to nicotine and other dopamine agonists, the magnitude of agonist activity by bupropion is fairly modest.[78,80] A higher dose of bupropion is available at 450 mg/day (BUP-450) that has demonstrated superior efficacy to BUP-300 for clinical conditions outside of smoking[14,16] with a favorable side effect profile but has not been tested for smoking cessation. BUP-450 could improve quit outcomes relative to the standard dose by generating more robust dopamine reuptake inhibition and other neuropharmacological effects,[81] which may in turn more strongly mitigate some underpinnings of relapse (e.g., reward processing, craving, nicotine reward). As anhedonic smokers' dopaminergic circuitry is particularly hypoactive, they may especially benefit from more robust dopaminergic agonism, which could surpass thresholds of neurotransmission necessary offset these processes[14] and improve quit success.

### A.9 High Dose Bupropion May Effectively Address the Problem of Post-Quit Residual Psychopathology

Quitting improves mental health with sustained abstinence.[82] Still, many smokers with anhedonia or other problems have pre-existing psychiatric symptoms that range from mild to severe, and benefit from psychiatric treatments even with quit succes.[83] Bupropion improves anhedonia and related psychopathologies, including depression,[81] ADHD,[15] social anxiety,[84] and others.[85] BUP-300 already improves some psychiatric symptoms during cessation.[26] High dose BUP may produce more powerful effects, as 400-450 mg/day is often used successfully for psychiatric patients not responding to BUP-300 or other treatments[81] and more powerfully reduces anhedonia than BUP-300.[14] Hence, BUP-450 may have unique collateral benefits for improving mental health.

### A.10 High Dose Bupropion May Effectively Address the Problem of Post-Quit Weight Gain in SWPS

Post-cessation weight gain is common and predicts adverse cardiovascular and metabolic outcomes.[86,87] smokers with (vs. without) some psychiatric conditions have higher BMIs and high post-cessation weight gain.[88,89] Adjusting for various psychiatric symptoms, anhedonia has been shown to incrementally associate with poor weight loss treatment outcomes, metabolic diseases, and cardiovascular morbidity and mortality.[90-96]

A recent Cochrane review found that BUP-300 mitigates the magnitude of weight gain relative to PLA and varenicline, though effects were modest and not robust at long-term follow-up.[97] Bupropion may facilitate weight loss by suppressing appetite, decreasing food reward,[98] and increasing metabolic rate via action on mesolimbic dopamine and hypothalamic melanocortin systems.[99] One of the first large trials tested the dose dependency of BUP for weight loss and showed that 400 mg/day outperformed 300 mg/day.[16] Doses ≥400mg BUP has since been the primary dose studied for weight loss, with results supporting the efficacy of BUP (vs. PLA) in various studies (2%–10% of initial body weight),[16,17,100-103] including trials in depressed patients.[103] High dose bupropion recently garnered FDA approval for weight loss when combined with naltrexone. Because the efficacy of BUP is not dependent on a diet/behavioral weight loss intervention platform,[16,17,100-103] BUP-450 could prevent weight gain the smoking cessation context without weight loss counseling. Thus, high dose bupropion may prevent post-cessation weight gain better than other cessation treatments, particularly among the population of anhedonic smokers for which weight-related health consequences are of particular concern.

### A.11 Summary of the Significance of the Proposed Study

The proposed RCT of BUP-450 vs. BUP-300 aims to identify a viable method of offsetting tobacco-related health disparities facing SWPS and two other leading causes of morbidity and mortality—mental illness and excessive weight. Results will be readily translatable to real-world clinics, given the modest cost of BUP-450 and the existing prescribing practices of high dose BUP for weight loss and psychopathology. If BUP-450 does not outperform BUP-300 in quit outcomes but improves weight gain and/or mental health without additional side effects, the trial would still provide invaluable evidence of a new cessation treatment that is equally efficacious to a front line treatment (i.e., BUP-300) but has superior metabolic and/or mental health benefits.

## B. INNOVATION

**Transdiagnostic approach to personalized medicine for SWPS.** As the first pharmacotherapy trial targeting a transdiagnostic vulnerability and its mechanisms of relapse risk, this research may facilitate a paradigm shift in personalized medicine cessation treatment for SWPS. By transferring focus from psychiatric diagnoses to transdiagnostic processes, a template for future cessation research targeting other promising transdiagnostic factors could be enabled (e.g., impulsivity, affective lability, anxiety sensitivity, executive dysfunction).

**First ever test of high dose bupropion for cessation.** No prior or ongoing smoking trial has tested high dose bupropion according to our search of the literature, NIH Reporter, and clinicaltrials.gov. Typically, after a new efficacious cessation treatment is identified (e.g., varenicline), considerable follow-up research ensues by nu-

merous research groups to broaden the treatment's reach and applications. Pending a positive result in this trial, a new wave of multiple research programs may arise to extend knowledge of BUP-450's efficacy by studying who, when, and how it exerts its clinical effect (e.g., Is BUP-450 effective in general smoker populations, obese smokers, smokers with substance use disorder, in primary care? Do genes, sex, race, nicotine dependence, or other factors moderate of BUP-450 effects? Is BUP-450 enhanced in combination with varenicline, NRT, or specialized behavioral therapies? What are the neural mechanisms of BUP-450 effects on smoking?). Such a result could have a substantial scientific and clinical impact beyond this study.

**First cessation trial utilizing the XL Formulation**. To date, the standard sustained release (SR) formulation, which requires twice daily dosing, has been the only BUP formulation studied in smoking cessation. There is now an extended release (XL) formulation of BUP-450 that is FDA approved, requires once daily dosing, and can be purchased as a 'generic' at low-cost. Thus, treatment adherence with once daily XL BUP may be higher than the SR formulation. Once daily BUP XL formations have shown comparable bioavailability to standard sustained release at twice per day[81] and clinical efficacy in clinical trials of psychiatric treatments, providing a scientific premise for utilizing XL. [15,104]

**Broadening the reach of mental health and weight loss treatment in cessation**. While many smokers are interested in cessation aids, most may not seek mental health treatment due to a failure to self-identify their own psychiatric symptoms and/or fear of stigma.[105] Other SWPS may delay cessation because of concerns about losing smoking as a method of coping with psychiatric symptoms.[106] Seeking weight loss treatment at the time of cessation is also rare because many smokers who ultimately gain weight post-cessation may not be concerned about their weight going into a quit attempt. Smokers concerned about post-quit weight gain may delay cessation or prioritize cessation over weight control. If BUP-450 improves secondary outcomes, we will have identified an innovative low-burden treatment that may: (a) broaden the reach of weight loss and mental health treatment to those who may otherwise not be treated; and (b) encourage quitting in smokers who may otherwise delay making a quit attempt due to post-quit weight gain or mental health concerns.

**Test of novel reward processing mechanisms of action.** Superimposed on this clinical trial, we will use state-of-the science low-burden laboratory methods to measure processing of reward-associated stimuli and collect novel self-report data on reward-oriented behavior outside the lab (C.6). By doing so, we aim to identify a novel mechanism of action of bupropion and smoking relapse risk that is plausible based on corresponding preclinical and human laboratory data, but has yet to be determined in the context of a real-world quit attempt.

**Extended pre-quit run-in treatment regimen.** The standard bupropion regimen involving a one week pre-quit run-in prior to the quit date may be insufficient for maximizing clinical outcomes because: (1) bupropion and its dopaminergic agonist metabolite hydroxybupropion do not reach steady-state concentrations until 5–8 days of treatment;[107] (2) more frequent smoking under bupropion-induced attenuation of nicotine reward may facilitate extinction of smoking behavior and improve bupropion's efficacy;[70] and (3) bupropion-induced attenuation of anhedonia and some of bupropion's other antidepressant effects often take 3-4 weeks to emerge.[81] The proposed trial will apply a novel 4-week extended pre-quit run-in treatment regimen that may be more sensitive to detecting bupropion's efficacy than the standard 1-week run-in, as evidenced by a prior trial of BUP-300 demonstrating superior quit outcomes with a 4-week (vs. 1-week) pre-quit run-in.[70]

**Cessation milestones.** PPA amalgamates several distinct milestones of the cessation process that may be underpinned by distinct mechanisms: (1) starting the quit attempt and establishing >24 abstinence vs. avoiding quitting altogether; (2) maintaining continuous abstinence vs. lapsing; and (3) amongst lapsers, recovering abstinence vs. relapse back to regular smoking patterns. In our prior work, BUP-300 improved establishment of abstinence, prevented lapse, but did not shorten time from lapse to relapse among lapsers,[108] and post-quit anhedonia predicted worse outcomes for all three milestones.[57] Supplemental analyses will test the effect of BUP-450 on milestones to elucidate how this novel treatment exerts its effects in anhedonic smokers (C.7).

**Measurement of body fat composition outcomes.** For the small subset of cessation trials that do report weight-related outcomes, body weight is the predominant index, which is an unreliable measure of adiposity due to regular fluctuations in water retention and muscle changes that may take place during cessation. In an innovative application of obesity research to smoking, we will use a bioimpedance monitor to accurately index body fat and muscle composition via electrical conductance in a non-invasive 2-min scan. As such, we anticipate greater sensitivity and clinical significance for detect for detecting a pro-metabolic effect of BUP-450.

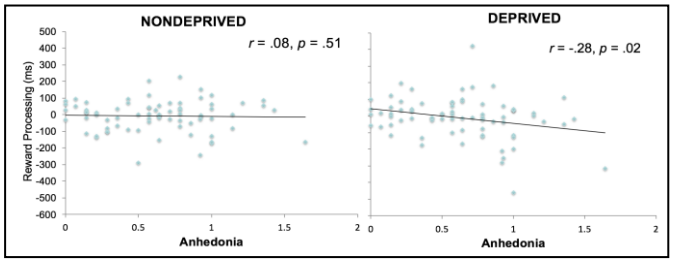
## C. APPROACH

### C.1 Progress Report for R01-DA26831, Project Period: 8/15/09 – 11/30/13

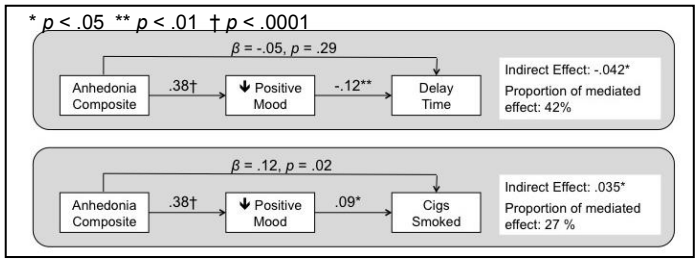
**Background.** The first period supported a laboratory study of how 16 hours of abstinence diminishes reward processing, which in turn promote reinstatement of smoking on a laboratory analogue measure of relapse. The goal was to examine whether this risk pathway was disproportionately prominent in anhedonic smokers.

**Addressing aims.** By the end of the period, we successfully achieved the originally stated aims of this project. Two-hundred eighty-five participants completed the entire 3-visit study protocol, which more than doubled our a priori accrual recruitment goal of 128. Results showed that smokers with higher anhedonia exhibited greater abstinence-induced deficits in the non-drug reward processing and lapse behavior on several outcomes.

**Leventhal et al. (2012). *Psychopharm, 222*(2), 343-351. Anhedonia predicts deficient processing of cues signaling social reward in nicotine abstinent but not nicotine sated states**. Nicotine was predicted to offset pre-existing anhedonia-related reward processing deficits that were expected to become expressed and exacerbated during abstinence. We tested examined whether anhedonia predicted diminished cognitive processing of stimuli signaling social reward (happy facial expressions) in nicotine deprived but not nondeprived states using a novel task we previously developed (and intend to use in the proposed trial; see C.6). Results supported the conclusion that among anhedonic smokers, disrupted reward was offset when nicotine sated, but expressed and exacerbated upon abstinence, suggesting that treatments that alleviate reward processing deficits exacerbated in upon quitting may promote cessation in anhedonic smokers.




**Leventhal et al. (2014). *J. Abnorm. Psychol., 123*(2), 375-386. The association of anhedonia with (re)lapse behavior is mediated by deficient positive mood state.** In this analysis of the relapse analogue task, higher anhedonia predicted behavior indicative of greater propensity toward lapse (i.e., quicker smoking initiation; $\beta$=-.10, $p$=.03) and relapse (i.e., more cigarettes purchased when given the opportunity to smoke; $\beta$=.13, $p$=.003). These relations were robust to control for depressive symptoms, anxiety, cig/day, and nicotine dependence, partially mediated by low positive mood states, and amplified by abstinence among those who responded the abstinence manipulation, $\beta$=.23, $p$=.004. Consequently, we infer red that treatments which raise positive affect may buffer the vulnerability to relapse facing anhedonic smokers.




**Guillot et al. Manuscript under review**. We examined anhedonia as a predictor of the pleasantness of smoking-related stimuli presented via computer. Across both abstinence conditions anhedonia was associated with marginally greater positive affective reactivity to smoking-related stimuli ($\beta$=.19, p=.06). These associations were not moderated by abstinence. We concluded that anhedonia may enhance the salience to cues that signal smoking reward during pre- and post-quit and treatments that block the reward response to smoking (e.g., bupropion) may benefit anhedonic smokers and perhaps offset with vulnerability to relapse.

**Leventhal et al. (2013). *Drug. Alcohol Depend., 133, 324-9.* Anhedonia, but not other manifestations psychiatric distress, predict greater abstinence-induced deficits in acute positive affective states.** In this analysis, we aimed to determine whether certain symptomatic expressions of depressive disturbance were associated with unique affective patterns of tobacco withdrawal. We found that anhedonic depressive symptoms (e.g., diminished interest, lack of pleasure) predicted larger abstinence-induced decreases in acute positive affect only ($\beta$s .17-.20). Depressive distress symptoms (e.g., sadness, worthlessness) predicted greater abstinence-induced increases in acute negative affect only ($\beta$s .24-.25). This study provided further evidence that treatments that counteract deficient positive affect during the cessation process may particularly benefit anhedonic smokers and also supported the broader transdiagnostic framework of not amalgamating symptoms by syndrome when studying the determinants of smoking among SWPS.

**Output beyond testing study aims.** We also leveraged the data to examine whether tobacco withdrawal or smoking reward are altered as a function of psychopathologies and other transdiagnostic vulnerabilities (e.g., hostility, anxiety sensitivity, negative urgency, PTSD symptoms, ADHD symptoms; see publication report). The study and dataset was a highly effective means of facilitating trainee career development. The data from this project produced 18 papers that first-authored by trainees, a successful dissertation, benefited post-doc who authored 6 papers and now has a tenure track position. Furthermore, Dr. Pang (Co-I), who a post-doc dur-

ing the prior funding period, author 10 papers from this project and leveraged the data to develop her own research program on sex differences in tobacco addiction in some analyses comparing men and women.[109,110] These efforts positioned her to obtain a K01 award on ovarian hormones and other female-specific factors in tobacco addiction (K01-DA040043; PI-Pang) and a faculty position at USC. During participant recruitment, we were able to tap into a very diverse population of smokers. Owing to the large number of African-American participants we recruited who successfully completed the study protocol (N=151; 53% of sample), we were able to leverage the data to successfully compete for a new 5-year $2M ACS grant to study the genetics of the laboratory tobacco withdrawal phenotype (RSG-13-163-01; PI-Leventhal) to expand of our sample to N=770 African American smokers (Current accrual N=615). Because the PI's lab has been focused on executing this fairly large study as well as another 5-year NIDA grant (R01- DA03396), there was not enough sufficient effort allocation or lab space available to move ahead with a competitive renewal for the proposed project. Hence, **the delay between the prior funding period and the proposed start date for this period was due to a lack of availability in space and effort allocation and not due to a lack of interest or productivity in the current research program**. The ACS and other NIDA R01 projects are slated to end in 2017 and 2018, making now an ideal time to pursue the proposed continuation period.

**Summary.** In total, the project produced 27 peer-reviewed publications, stimulated two new 5-year grants, substantively impacted trainee career development, and provided clear evidence of treatment targets for anhedonic smokers. This competitive renewal reflects a direct translation of these efforts to treatment development, which we hope will be part of a long-standing program that produces high-impact data on the nature and treatment of tobacco addiction, psychopathology, and their comorbidity.

## C.2 Preliminary Studies Not Covered in the Progress Report

**Expertise of investigators.** The team members have an outstanding record of collaboration and productivity (i.e., 37 co-authored papers[8,35,46,109-142] and 7 collaborative grants [R01-DA03396, R21-DA034768, R01-DA033296, ACS-RSG-13-163-01, K01-DA040043, R21-DA02983]). Dr. Leventhal (PI) has expertise in affective science, psychiatric comorbidity with smoking, and nicotine psychopharmacology and forged major theory and research advances on transdiagnostic vulnerabilities in smoking. Dr. Strong (Co-I) is an expert in smoking cessation treatment research, methods, and data analysis. He has been the primary methodologist and statistician for 8 externally-funded cessation clinical trials, including a BUP-300 trial (R01 DA007770) and his own trial for depressed smokers (R01 DA017947; PI-Strong), and will oversee analysis for the proposed study. Dr. Ray (Co-I) is an expert in neuropharmacology and medication development for addictions. She has led several alcohol pharmacotherapy trials, including a cessation pharmacotherapy trial for heavy drinking smokers (R01- DA041226; PI-Ray, Co-I Leventhal). She will help with accrual (see below) and will position the research to address mechanistic insights and position the work to address addictions more broadly. Dr. Pang (Co-I) is a neuroscientist with expertise in the psychobiological underpinnings of sex differences in nicotine addiction. She will ensure that this research ideally addresses sex as a biological variable. Dr. Hong (Co-I) is an internist and physician scientist with expertise in obesity research. He directs a highly active outpatient obesity clinic within USC Internal Medicine. As a clinician who regularly prescribes BUP-450, Dr. Hong provides the ideal perspective to ensure the results translate to practice. He will also provide medical oversight.

**Anhedonia as a contributor to smoking dependence and relapse.** Dr. Leventhal found that rates of anhedonia were higher among psychiatric outpatients with current (*n*=352) vs. past (*n*=211) nicotine dependence (59.4% vs. 47.4%, *p*=.006),[35] suggesting that anhedonia may contribute to difficulty quitting smoking in SWPS. In an analysis of psychopathologic dimensions as risk factors for relapse in a cessation trial (N=157), he found that pre-quit anhedonia predicted worse outcomes at 8, 16, and 26 week post-quit incrementally to somatic complains, negative affect, interpersonal problems, nicotine dependence, cig/day, and history of MDD ($p$ = .002).[56] Dr. Leventhal also found that among non-treatment seeking smokers (N=212), anhedonia was correlated with number of past failed quit attempts ($r$=.28, $p$=.0007) and proportion of quit attempts that ended in rapid relapse <24hr ($r$=.20) controlling for negative affect.[8] In a lab component of the aforementioned study, anhedonic (vs. non-anhedonic) smokers were more sensitive to the effects of nicotine deprivation the urge to smoke for pleasure (Anhedonia × Deprivation, $p$=.03), which is examined as a mediator in this trial (C.6). In the Wisconsin Smokers Health Study (WSHS) trial (N=1,504), Dr. Leventhal found that a single lifetime anhedonia item, which we plan to use in the proposed trial to classify anhedonic smokers, predicted greater odds of relapse at 8- and 26 weeks post quit PPA (OR=1.42, $p$=.004).[45] Even in analyses controlling for depressed mood, MDD, recurrent MDD, dysthymia, anxiety disorder, substance use disorder, nicotine dependence, and sex, quit rates were lower in anhedonic (vs. non-anhedonic) smokers. An analysis of a daily diary anhedonia measure in the WSHS showed that anhedonia at various time points pre and post-quit predicted failure to ces-

sation reach 3 cessation milestones, and relapse even amongst those given NRT.[57]

**Bupropion's efficacy and mechanisms of action for smoking cessation.** Dr. Leventhal contributed to analyses of WSHS data showing that BUP-300 promotes initiation of quitting, prevents lapse, and improves 8-week PPA. Dr. Strong served as the primary methodologist in the Zyban Collaborative Trial (ZCS; N=524), which showed that BUP-300 (vs. PLA), but not CBT for depression (vs. standard) cessation counseling, improved cessation outcomes in smokers with elevated depressive symptoms (OR = 1.97, $p$<.0001).[3] In collaboration with Dr. Leventhal, he found that reductions in positive affect pre- and post-quit increased relapse risk in two trials,[143] and that urge mediated BUP-300's efficacy. In analyses of ZCS and other trials, Drs. Leventhal and Strong found that dopamine-related gene variants moderated BUP-300's efficacy.[139,141]

**Obesity, psychopathology, pharmacotherapy, and smoking.** Dr. Leventhal has shown that nicotine dependence buffers the association between MDD and obesity, suggesting that depressed individuals may turn to smoking to offset the effects of MDD on obesogenic behaviors.[144] Dr. Strong has participated in several weight loss and obesity trials[145-147] and has shown that obesity moderates the efficacy of NRT in women rendering NRT ineffective for obese female smokers.[148] Dr. Pang has shown that female smokers have stronger motives to smoke for mood-regulation than male smokers.[110] Dr. Ray has done extensive research documenting the efficacy and mechanisms of naltrexone and other drugs for alcohol, smoking, and other addictive disorders in laboratory and clinical trial studies.[127,149-154] Dr. Hong has published a series of clinical studies of the efficacy, mechanisms, and predictors of obesity treatments,[155-158] including a recent paper showing that high dose bupropion's effects on weight loss are not dependent on drug-induced nausea.[159] In sum, Drs. Leventhal, Strong, Ray, Pang, and Hong have collectively produced an extensive body of work that has advanced understanding and treatment of nicotine addiction, psychopathology, weight loss, and their comorbidity and are therefore poised to successfully execute the proposed research.

## C.3. Design Considerations

**Rationale for selecting BUP-300 as the sole active medication comparison.** As the initial test of BUP-450 for cessation, the first question is whether BUP-450 outperforms the standard dose. Comparing BUP-450 to other front-line medications (e.g., varenicline, NRT) will be essential next steps in this line of research; yet, the sample size needed to be sufficiently powered to compare BUP-450 to BUP-300 and other active treatments is currently cost prohibitive and will be warranted pending demonstration of superiority of BUP-450 vs. BUP-300.

**Why no combination pharmacotherapy**? BUP-300 with varenicline may be more effective than BUP-300 alone.[160] BUP-300 with (vs. without) NRT comparisons are equivocal.[26] Testing whether in combo vs. monotherapy for BUP-450 is of interest, but would require twice the sample. One option would be to test BUP-450 vs. BUP-300 both in combination with another medication. Yet, including another treatment could washout dose effects or leave unclear whether dose differences are caused by synergism with the other treatment or stand-alone efficacy. Such a result would limit translation cases in which combo-therapy is not viable.

**Type of counseling**. We opted against intensive treatments, including those that address psychopathology or weight loss because they: (a) require additional counselor training, more patient burden and can be difficult to translate into clinical settings; (b) have not improved anhedonia or quit rates in anhedonic smokers (A.7);[74,75] (c) may not be well accepted by smokers not wishing to focus on psychiatric issues or weight in a cessation counseling context; and (d) do not affect the efficacy of BUP-300 for cessation or weight loss.[3,100] Instead, we use a brief and effective quit smoking protocol based on USDHHS practice guidelines.[161]

**Operational definition of "anhedonic" smokers.** We will classify smokers as anhedonic based on response to a brief single anhedonia item on the Patient Health Questionnaire-2 (PHQ). The PHQ is among the most widely adopted mental health screening measures in primary care[162] and is nearly identical to the SCID-5 and CIDI Anhedonia item used in psychiatric settings. Thus, classifying smokers as anhedonic and likely to benefit from BUP-450 will be highly translatable. Despite psychometric limitations of single-time measures, responses to a single-item anhedonia measures robustly differentiated cessation outcomes in our prior work.[45] A standard multi-item anhedonia scale will be included as a secondary measure (C.6). The PHQ has lifetime and current assessment frames and can use unrestricted or stringent duration thresholds ($\geq$2 weeks). Though requiring anhedonia to be current and be of longer duration could exclude those with less-severe anhedonia, we opted for a more sensitive measure (i.e., any lifetime anhedonia) with a 43% prevalence rate in smokers[44] because: (1) fewer people endorse current/chronic than lifetime anhedonia, restricting generalizability to a smaller population; (2) lifetime anhedonia robustly predicts cessation outcomes,[45] (3) utilization of the any duration threshold (vs. 2+ weeks) does not affect relapse risk,[45] and (4) smokers with lifetime anhedonia who do not express

anhedonia at the time of quitting may experience anhedonia post-cessation and are therefore important to capture.[57]

**Why no non-anhedonic comparison?** We predict BUP-450 vs. BUP-300 effects are greater in anhedonic smokers (anhedonia × treatment interaction). To test this, a comparison group of non-anhedonic smokers would be needed, which would double the N. Given this is the first RCT in anhedonic smokers and first test of BUP-450 we first establish efficacy in this high risk group and then can follow-up with larger scale multi-group trials. Instead, we examine baseline anhedonia level amongst anhedonic smokers as a moderator (Aim 2; C.7)

**Why not target overweight smokers?** Evidence examining pre-quit weight status as a moderator of post-cessation weight gain are equivocal, although normal and over-weight smokers both exhibit significant post-cessation weigh gain.[163-172] Thus, targeting overweight smokers may be unnecessary and restrict generalizability. Instead, BMI will be balanced across conditions (C.5) and tested in moderator analyses (C.7).

**Why begin with a pilot trial?** Small pilot trials are sometimes conducted prior to full RCTs, which we plan to do for this trial. Experts conclude that such trials are useful for staff training, solidification of protocol procedures, and modification of logistical methods to maximize data collection efficiency and integrity (e.g., methods to uphold study blind).[173] As the standard clinical and scientific practices for bupropion treatment leave no substantive methodological or clinical questions, a small pilot (N=30) will be used primarily for this purpose rather than for major developmental or formative reasons. Effect size estimated based on highly stable effects of relevant prior research with BUP-300 and BUP-450 (C.8).

**What about within-condition pharmacokinetic/pharmacodynamic variation in drug response?** Genetic variants, biomarkers, and patient factors may introduce variance in bupropion metabolism, pharmacodynamics, and clinical outcomes,[174-177] which is important in a dose-response study. It is premature to include such factors a priori in the study design, given the state of the literature. Formative laboratory research with clinical proxies (e.g., craving) could ultimately inform RCTs accounting for such factors, but would slow translation. Instead, we will bank biospecimens for possible future assays (e.g., *CYP2B6* genotype, nicotine metabolite ratio) pending funding and address patient characteristics (e.g., BMI, sex) in secondary moderator analyses.

**Treatment and follow-up length.** BUP-300 (vs. PLA) effects at 12 vs. 6 months do not differ[26] and risk of relapse due to anhedonia emerges early.[45,56] Thus, we selected a 6-month follow-up. Differences in outcome by length of BUP-300 are modest (7 vs. 11 wk post-quit).[80] We thus chose 8-weeks post quit (+ 4-wk run-in).

## C.4 Participants and Recruitment

**Study site.** All visits will take place at the USC Health, Emotion, & Addiction Laboratory (USC-HEAL) clinical research facility at USC Medical Center northeast of downtown Los Angeles, which is highly accessible via public transportation. USC-HEAL studies have successfully retained 1500+ daily smokers in the past 7 years. For all HEAL studies (currently there are 5), smokers are screened via a highly-efficient centralized calling center, which screens ~180 smokers per month, and places them into the appropriate study given eligibility.

**Recruitment and timeline.** We plan 3 months for startup, 9-months for an initial pilot, 31 months for primary trial accrual, 8 further months to complete data collection and follow-ups, and 9 months for analysis and write-up. A pilot study with be done on a subset of participants (randomize N=15 per condition) to refine procedures. The pilot will utilize the same design as the standard trial, with non-essential assessments being abbreviated for logistical purposes. Based on prior work and the efficient phone screening methods,[3] we expect 16% to be ineligible at the in-person screening and 13% of consenting subjects to not complete all pre-randomization visits and be replaced. Conservatively estimating 80% eligibility and 85% randomization, 14 second-stage screens per month are needed to obtain the intent-to-treat sample of 300 randomized smokers, which had been obtained our prior 5-year trial[3] using the recruitment strategies proposed here. The study will be announced via online, print, and mass media advertisements in the greater Los Angeles metropolitan area. Targeted recruitment will take place through: (1) existing research databases from USC-HEAL and Dr. Ray's (Co-I; UCLA) Laboratory, which contain contact information for 2000+ daily smokers in the LA metro who wished to be called about future studies; (2) referrals from USC primary care clinics run by Dr. Hong (Co-I) and his colleagues; and (3) participants responding to advertisements to other USC-HEAL studies that are eligible for this trial..

**Eligibility criteria**. Inclusion: (1) Lifetime anhedonia on the PHQ-2; (2) smoking 10+ cig/day for 2+ years; (3) Aged 21-65 (21 is legal age to purchase tobacco in CA); (4) breath carbon monoxide (CO) $\geq$ 10 ppm Exclusion: (a) past year moderate or severe DSM-IV non-tobacco substance use disorder (4+ symptoms); (b) a conservative definition of drug contraindications based on lifetime history of panic, bipolar, psychosis, bulimia nervosa, anorexia nervosa, seizure disorders, suicidal attempt (b) report of past 90-day suicidal ideation and alco-

hol withdrawal, (c) unstable cardiovascular disease (unstable angina; recent stroke/TIA < 90 days) or uncontrolled hypertension (blood pressure > 150/90), (d) severe renal/hepatic impairment based on serology evaluation ( eGFR <30, AST/ALT >= 3x ULN), (e) current use of other cessation medications or counseling, (f) current use of e-cigarettes or other tobacco products ≥2 times/week, (g) recent use of bupropion containing products < 90 days, (h) current anti-psychotic, anxiolytic, antidepressant, or psychostimulant medication; (g) currently or plan to be pregnant (based on urine HCG) or active breastfeeding.

**Sex/ethnicity.** We expect our sample will parallel the diversity of Los Angeles County, as in samples collected in our prior research (3% Asian, 53% Non-Hispanic Black, 37% White, 7% other, 13% Non-Black Hispanic),[9] and balanced on sex. Targeted recruitment will be applied to ensure adequate representation of each group.

**Retention.** Retention procedures involve: (1) escalating incentives for follow-ups ($25, $50, $75, $150); (2) incentives for baseline assessment and completing supplemental measures for mediator hypotheses ($25 per visit); (3) obtaining social networking user contact info, emails, phone numbers of close friends/relatives to track participants not reachable via personal cellphone; (4) keeping participant burden as low by limiting visits and measures to what is scientifically and medically necessary; and (5) permitting phone counseling when possible. Using similar procedures in previous trials we have been involved in, 81.3% of subjects completed all follow-ups and 2.3% were entirely lost to follow-up in a 12-month BUP-300 trial.[3] In a fluoxetine trial we took part in with an extended 8-week pre-treatment run-in, only 6.5% were lost to follow-up.[21]

## C.5 Procedure

**Screening.** After phone screen, an in-person screening will include both written and verbal informed consent, psychiatric interview, breath CO, urine pregnancy test, blood collection for labs, baseline assessments (C.6), and medical screening involving a physical exam. At the start of the baseline visit, the project team will explain the study and obtain written consent to participate. The study physician will review the medication with participants and obtain additional verbal consent to participate after reviewing the study treatment. Those ineligible will be provided referral information for psychiatric, addiction, family planning/OB (if appropriate) and smoking cessation (California quit line) resources. For participants who report past 30-day suicidal ideation, a suicide assessment screening protocol will involve a systematic assessment for emergent events, as well as referral to emergency mental health treatment and referral to a suicide prevention crisis hotline. In cases in which participants endorse current suicidality on the SCID-NP, Dr. Leventhal (or an available commensurately trained clinician if Dr. Leventhal is unavailable) will be called and will conduct a suicide risk assessment and protocol with the participant If the participant appears at high risk and/or cannot contract for safety, emergency services will be called. To further monitor risk for suicide and/or self harm, study staff will review all questionnaire items that enquire about the presence of suicidal thoughts or ideations.

**Randomization.** Eligible participants will be randomized in a 1:1 ratio using urn randomization[178] for balance on sex, level of nicotine dependence (Fagerström Test for Nicotine Dependence; FTND),[179] BMI, and current anhedonia level (Snaith Hamilton Pleasure Capacity Scale; SHAPS)[180] across conditions.

**Schedule.** Participants will attend a pre-treatment visit involving eligibility screen and baseline measures (1-2 visits depending on physician availability), 7 in-treatment, and 3 post-treatment follow-up visits (C.6). On some visits subjects will complete supplemental measures of mediators (C.6). Certain visits will occur via phone if preferred by participant (Table).

| Week | Pre-R** | -4 | -2 | -1 | 0 | 1 | 2 | 4 | 5-7 | 8 | 16 | 26 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Pre-quit Tx | | | Post-quit Tx | | | | | Post-tx F/U | | |
| Counseling | | X | X | X* | X | X* | X* | X | | | | |
| Medical visit/labs | X*** | X | | | | | | | | X*** | | |
| Medication | | X | X | X | X | X | X | X | | X | | |
| Core Ax | | X | X | X | X | X | X | X | | | | |
| Supplemental Ax | | X | X | | X | | | X | | | | |
| Outcome Ax | X | | | | | | | X | | X | X | X |

Week = from quit day (0). Ax = Assessment. F/U = follow-up. R = Randomizaiton. Tx = *Visit by can be by phone. **Additional baseline measures (see C.6). ***Body adiposity scan

**Medication.** Formulation**.** Bupropion XL 150mg, and placebo tablets matching in appearance (Rejuvination Labs, San Diego, CA) will be used. Regimen. The selected regimen was based on medication guidelines[181] and evidence that a 4-week extended run-in prior to quit day produces superior outcomes relative to the standard 1-week run-in,[70] All dosing is once per day per XL formulation guidelines.[182] BUP-450 involves a 17-day up-titration (1 x 150 mg tablet for 3 days followed by 2 x 150 mg tablet for 14 days), 10-day pre-quit run-in (3 x 150 mg tablets), 8-week post-quit treatment period (3 x 150 mg tablets), and 1-week down-titration (2 x 150 mg tablet). The BUP-300 regimen is identical except that pre-quit run-in and 8-week post-quit treatment period involves 1 x placebo + 2 x 150mg to match number of tables taken across conditions and differentiate dose. Clinical monitoring/safety*:* In addition to eligibility screen, participants will meet with the physician at: (a) treatment outset to review the medication, managing and/or reporting side effects, pregnancy contraindications, and rationale for taking the medication for ≥4

weeks prior to quitting; and (b) end of treatment to review treatment, collect labs, and discuss down-titration. All participants will be given a 24-hour phone number and physician office hours will be available as needed. Vital signs, weight, and side effects, including suicidal ideation, will be monitored at each study visit. In the event that significant medical problems are encountered, the blind will be broken and appropriate medical treatment will be provided.

**Cessation counseling.** All participants will offered bibliotherapy (NCI- Clearing the Air)[183] and receive seven 10-20 min sessions based on the USDHHS clinical practice guidelines. Trained counselors (blind to treatment), supervised by Dr. Leventhal, a licensed clinical psychologist, will provide the counseling, which focuses on enhancing social support, problem solving, coping skills, and check-ins on medication adherence. Three pre-quit visits focus on establishing the quit-date and preparation. Four post-quits focus on reinforcing abstinence (or encouraging the resumption of cessation) and continued support. There is a final check-in at the end of the medication treatment period. Some visits will be offered via phone (Table).

**C.6 Measures (see Table for the assessment schedule).**

**Screening and baseline measures.** (1) Medical history interview for bupropion contraindications; (2) Physical exam; (3) Blood and urine for liver/kidney function, drug screen, and pregnancy; (4) EKG to rule out unstable cardiovascular disease; (5) Clinical Institute Withdrawal Assessment for Alcohol[184] to rule out alcohol-related seizure risk (score ≥ 10); (6) Structured Clinical Interview for DSM-5 (SCID) modules for diagnostic rule outs and other Axis-I disorders for descriptive purposes (PTSD, MDD, Dysthymia, Social Anxiety, ADHD)[185]; (7) Tobacco Product Use History Questionnaire (e.g., age of onset, cig/day, use of other tobacco products, etc.); (8) FTND;[179] (8) Ten-Item Drug Abuse Screening Test (DAST-10)[203], with no record made regarding specific names of drugs used,and (9) Premenstrual Symptoms Impact Survey[186] and date of last menstruation, given evidence that these factors influence quit outcomes[187] will be used in supplemental sex-specific analyses (C.7).

**Core assessments (all in-treatment visits).** To aid counselors' intervention, collect cessation milestone outcomes (C.7), and to monitor safety, we will administer: (a) smoking timeline follow-back to track smoking,[188] (b) 8-item Minnesota Nicotine Withdrawal Scale,[189] (c) Systematic Assessment for Treatment Emergent Events[190] and open ended reports coded by Medical Dictionary for Regulatory Activities Version 14.0.

**Supplemental assessments: mediators.** We will use a multi-method assessment strategy to tap multiple facets of reward processing and behavior that have shown sensitivity to the main effect of nicotine abstinence and differences in abstinence effects by anhedonia level:[9] (1) Self-report Tripartite Pleasure Inventory, which instructs participants to rate the extent of pleasure, frequency of engagement and desire for (irrespective of engagement) 12 typically-enjoyable activities during the past week,;[191] (2) The Emotional Interference Gender Identification Task,[192] which examines social reward processing by measuring extent to which the pictures of actors displaying happy (relative to neutral or angry) facial expressions on a computer capture one's attention and consequently distract and slow the speed of identifying the actor's gender by pressing a corresponding key (10 min); (3) A reward learning task,[193] which measures the extent to which respondents modulate their behavior in response to reward. Participants will be asked determine length of visual stimulus presented on the screen by pressing a key (long or short; the actual difference is difficult to judge). One response will be differentially reward at $.05 per trial relative to the other. The extent to which choices become biased towards the more rewarded choice reflects the degree of reward learning (10 min; (4) The 5-item Brief Questionnaire of Smoking Urges (QSU)[194] Factor 1 scale of desire to smoke for pleasure; (5) The 10-item Positive and Negative Affect Schedule (PANAS)[195] positive affect scale. To examine discriminant validity of effects, we use the 5-item QSU Factor 2 measure of desire to smoke for negative affect relief, and the PANAS negative affect scale.

**Outcome assessments (Baseline, 4-wk, 8-wk, 16-wk, 26-wk).** Primary outcome: Point prevalence abstinence (PPA) self-report of no smoking or use of any other tobacco products (including e-cigarettes) in past 7-days (not even a puff) verified by salivary cotinine ≤10 ng/ml is our primary outcome. Secondary outcomes: (a) Smoking cessation milestones derived from Smoking Timeline Follow Back interview (i.e., achieving ≥24 hr abstinence, days to lapse, days from lapse to relapse; C.7), (b) The 29-item Inventory of Depressive and Anxious Symptomatology[196] Social Anxiety, General Depression, Traumatic Intrusions subscales; (c) 18-item Adult Self-Report Scale for ADHD[197] adapted for past-week symptom assessment; (d) SHAPS anhedonia scale,[180] (e) objective body weight via a medical-grade scale; (d) adiposity via bioimpedance monitor (InBody520, GE Healthcare)—a non-invasive 2-min scan that analyzes body electrolytes to yield fat, muscle, and water composition estimates, which we will use to generate percent body fat outcomes. In addition to self-reports of medication adherence, detectable bupropion, >5ng/mL in urine[198] during study visits will be used as a supplemental marker. Though participants will be told to avoid use of other quit treatments, e-cigarettes, or tobacco/nicotine

products during the trial, these will still be assessed via self-report and participants who report transitioning to e-cigarettes will be analyzed as an exploratory intermediate outcome.

## C.7 Analytic Plan

**Preliminary Analyses.** Distributions will be examined to determine the need for normalizing transformations. Using ANOVA or $X^2$ test, we will examine if groups differ at pretreatment on relevant variables (despite randomization) to inform possible inclusion in analyses.

**Primary Aim 1: Smoking Outcome.** 7-Day biochemically-verified PPA (missing coded as smoking) at 4- 8- 16- and 26-week post-quit follow-up will be evaluated using individual latent growth curve models (LGCM) for longitudinal binary outcomes including planned covariates (FTND, sex, SHAPS anhedonia score, BMI), the main effects of medication (BUP-450 vs. BUP-300), and the effect of time. Non-linear effects of time will be explored using nested likelihood ratio tests prior to evaluating hypotheses. Treatment by time interactions will be examined to characterize medication effects before and after treatment termination. To understand at what stage of the cessation process the treatments exert their effects, we will also analyze cessation milestone outcomes of attaining abstinence (yes vs. no abstinent for >24hr in the first 2 weeks post-quit), days to lapse (i.e., first puff), and days from lapse to relapse (i.e., first puff until the onset of 7 consecutive days of smoking) using logistic and cox regression. Sensitivity analyses of treatment effects will examine medication adherence and counseling visit attendance as moderator of treatment effects and we will re-analyze primary models in the subset of fully-adherent participants. Additional comparisons of side effects between the conditions will be conducted to verify tolerability of BUP-450.

**Primary Aim 2: Mediation.** Aim 2 will examine slopes from individual piece-wise LGCMs (or raw difference scores when only 2 timepoints available) to model changes in reward processing (see C.6) prior to quit day, the jump from pre to 1-week post-quit, and post-quit changes. A latent variable framework using Mplus 7.4 will allow estimates of treatments on individual growth in mediators (path 'a') to be modeled jointly with effects of growth in likelihood of abstinence (path 'b') using models that limit bias in estimates and provide accurate evaluation of mediation using bias corrected effect estimation and product of coefficients procedures. We will attempt to create a composite that amalgamates all reward processing mediators using principal component analysis (PCA), or if a strong component is not detected, test each raw variable individually. We will model time to lapse first and other smoking outcomes secondarily with and without smoking as a time-vary covariate. Additional multiple mediator models adding all 3 growth pieces simultaneously and including the discriminant constructs (negative affect, urge to smoke to alleviate negative affect) will be test the specificity of effects.

**Secondary Aims:** Aim 3 will examine medication effects on anhedonia (SHAPS) and related psychopathology (i.e., depressive, social anxiety, ADHD, PTSD symptoms) and body weight and body fat percentage trajectories using individual growth models (intercept and slope) of assessments at visits during treatment. Moderation of the differential effect of treatment (Aim 4) will be assessed with interaction terms of treatment condition and corresponding moderators (SHAPS, depressive, social anxiety, ADHD, PTSD symptoms) in successive models as described above in LGCM.

**Supplemental analyses of the biological variable of sex and other characteristics (age, ethnicity/race).** Using the strategies above, we will examine if sex, ethnicity/race, and FTND moderate treatment effects on primary and secondary outcomes. We will report sex-stratified analyses and test, amongst women, whether days since menstruation at the onset of treatment and quit day moderates outcome using several classification methods (follicular vs. luteal; early follicular vs. late follicular vs. mid luteal vs. other).

**Missing data.** Prior to testing primary hypotheses we will conduct exploratory analyses to determine if baseline characteristics (e.g. sociodemographics, smoking) predict patterns of missingness. Any marginally significant ($p<.10$) predictors of missingness will be included as covariates in LGCM models above and used with multiple imputation methods for evaluating obtained model estimates.[199] Maximum likelihood estimation of multilevel models with Mplus has the advantage of using all available data. Mplus also incorporates special facilities for maximum likelihood estimation with data missing either completely at random, or data missing at random (missing data can be a function of observed covariates) with continuous, categorical, or count outcomes and facilitates analyses using multiply imputed data.

## C.8 Sample Size Considerations

We determined power/ sample size using an empirical power analysis.[200] Estimated PPA rates for BUP-450 (45%, 38%, 30%, 30%), BUP-300 (30%, 25%, 20%, 20%) at the 4-, 8-, 16- and 26-week assessments were based on previous literature, including Cochrane Review summaries of BUP-300 effects on quitting, known

relapse curves in anhedonic smokers, BUP-450 vs. BUP-300 vs. PLA effects on weight loss and mental health.[22,97,162] We generated 1,000 multivariate normal random samples of correlated binary outcomes using covariance estimates from prior trial data (range 0.55-0.25)[3] and analyzed the datasets using LGCM focusing on the proportion of significant ($p<0.05$) values for each pair-wise contrast (Aim 1). The percentage of datasets with significant effects for each hypothesis (i.e., >80% of ps < .05) provided a simulation-based estimate of power. Using this technique, we found that enrolling a sample size of 375 (BUP-450: N<150, BUP-300 N<150) conservatively would have power >0.83 to detect main effects when testing our primary hypothesis, allowing for 20% attrition among those enrolled. Parallel simulations were conducted using LGCM to assess power for growth trajectories in continuously scaled mediators assuming an effect of treatment dose response on reward processing (*d*s>0.3), and reward processing on outcome (*d*s>0.17) based on the prior literature.[131,140,201,202] We also found support for power >0.81 with average effects of 0.31 (sd=0.11) with N=375. Additional simulations for secondary mental health and body/weight adiposity outcomes based effects in prior literature (ds>0.3)[22,97,162] yielded adequate power (>.80). Missing individuals will be presumed to have continued smoking. All analyses will use an intent-to-treat approach.

## REFERENCES


1. Williams JM, Steinberg ML, Griffiths KG, Cooperman N. Smokers with behavioral health comorbidity should be designated a tobacco use disparity group. *American journal of public health.* 2013;103(9):1549-1555.
2. Piper ME, Smith SS, Schlam TR, et al. Psychiatric disorders in smokers seeking treatment for tobacco dependence: relations with tobacco dependence and cessation. *Journal of consulting and clinical psychology.* 2010;78(1):13.
3. Brown RA, Niaura R, Lloyd-Richardson EE, et al. Bupropion and cognitive–behavioral treatment for depression in smoking cessation. *Nicotine & Tobacco Research.* 2007;9(7):721-730.
4. Leventhal AM, Zvolensky MJ. Anxiety, depression, and cigarette smoking: A transdiagnostic vulnerability framework to understanding emotion–smoking comorbidity. *Psychological bulletin.* 2015;141(1):176.
5. Gorwood P. Neurobiological mechanisms of anhedonia. *Dialogues Clin Neurosci.* 2008;10(3):291-299.
6. Leventhal AM, Munafò M, Tidey JW, et al. Anhedonia predicts altered processing of happy faces in abstinent cigarette smokers. *Psychopharmacology.* 2012;222(2):343-351.
7. Leventhal AM, Ameringer KJ, Osborn E, Zvolensky MJ, Langdon KJ. Anxiety and depressive symptoms and affective patterns of tobacco withdrawal. *Drug and alcohol dependence.* 2013;133(2):324-329.
8. Leventhal AM, Waters AJ, Kahler CW, Ray LA, Sussman S. Relations between anhedonia and smoking motivation. *Nicotine & Tobacco Research.* 2009:ntp098.
9. Leventhal AM, Trujillo M, Ameringer KJ, Tidey JW, Sussman S, Kahler CW. Anhedonia and the relative reward value of drug and nondrug reinforcers in cigarette smokers. *Journal of abnormal psychology.* 2014;123(2):375.
10. Nutt D, Demyttenaere K, Janka Z, et al. The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. *Journal of Psychopharmacology.* 2007;21(5):461-471.
11. Prices for Brand Name Drugs Under Selected Federal Programs. Congress of the United States; 2015. https://www.cbo.gov/sites/default/files/06-16-prescriptdrug.pdf. Accessed July 13. 2015.
12. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev.* 2013;5(5).
13. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *The Lancet.* 2016.
14. Tomarken AJ, Dichter GS, Freid C, Addington S, Shelton RC. Assessing the effects of bupropion SR on mood dimensions of depression. *Journal of affective disorders.* 2004;78(3):235-241.

15. Wilens TE, Haight BR, Horrigan JP, et al. Bupropion XL in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled study. *Biological psychiatry.* 2005;57(7):793-801.
16. Anderson JW, Greenway FL, Fujioka K, Gadde KM, McKenney J, O'neil PM. Bupropion SR Enhances Weight Loss: A 48-Week Double-Blind, Placebo-Controlled Trial. *Obesity Research.* 2002;10(7):633-641.
17. Settle EC, Stahl SM, Batey SR, Johnston JA, Ascher JA. Safety profile of sustained-release bupropion in depression: results of three clinical trials. *Clinical therapeutics.* 1999;21(3):454-463.
18. Lawrence D, Williams JM. Trends in Smoking Rates by Level of Psychological Distress—Time Series Analysis of US National Health Interview Survey Data 1997–2014. *Nicotine & Tobacco Research.* 2016;18(6):1463-1470.
19. Hertzberg MA, Moore SD, Feldman ME, Beckham JC. A preliminary study of bupropion sustained-release for smoking cessation in patients with chronic posttraumatic stress disorder. *Journal of clinical psychopharmacology.* 2001;21(1):94-98.
20. Hall SM, Tsoh JY, Prochaska JJ, et al. Treatment for cigarette smoking among depressed mental health outpatients: a randomized clinical trial. *American journal of public health.* 2006;96(10):1808-1814.
21. Brown RA, Abrantes AM, Strong DR, et al. Efficacy of sequential use of fluoxetine for smoking cessation in elevated depressive symptom smokers. *nicotine & tobacco research.* 2014;16(2):197-207.
22. van der Meer RM, Willemsen MC, Smit F, Cuijpers P. Smoking cessation interventions for smokers with current or past depression. *The Cochrane Library.* 2013.
23. Piper ME, Cook JW, Schlam TR, Jorenby DE, Baker TB. Anxiety diagnoses in smokers seeking cessation treatment: relations with tobacco dependence, withdrawal, outcome and response to treatment. *Addiction.* 2011;106(2):418-427.
24. Piper ME, Schlam TR, Cook JW, et al. Toward the Development of Precision Smoking Cessation Treatment I: Moderator Results from a Factorial Experiment *Manuscript under review.*
25. Kahler CW, Brown RA, Ramsey SE, et al. Negative mood, depressive symptoms, and major depression after smoking cessation treatment in smokers with a history of major depressive disorder. *Journal of abnormal psychology.* 2002;111(4):670.
26. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *The Cochrane Library.* 2014.
27. Hitsman B, Papandonatos GD, McChargue DE, et al. Past major depression and smoking cessation outcome: a systematic review and meta-analysis update. *Addiction.* 2013;108(2):294-306.
28. Watson D, O'Hara MW, Chmielewski M, et al. Further validation of the IDAS: evidence of convergent, discriminant, criterion, and incremental validity. *Psychological assessment.* 2008;20(3):248.
29. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. *Neuropsychopharmacology.* 2004;29(10):1765-1781.
30. Leventhal AM, Zvolensky MJ, Schmidt NB. Smoking-related correlates of depressive symptom dimensions in treatment-seeking smokers. *Nicotine & Tobacco Research.* 2011;13(8):668-676.
31. Krueger RF, Markon KE. Reinterpreting comorbidity: A model-based approach to understanding and classifying psychopathology. *Annual review of clinical psychology.* 2006;2:111.
32. Ameringer KJ, Chou C-P, Sussman S, Unger JB, Leventhal AM. Identifying Shared Latent Dimensions of Psychological Symptoms: Implications for the Psychological Correlates of Smoking. *Journal of psychopathology and behavioral assessment.* 2015;37(3):454-468.

33. Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the united states: results from the national epidemiologic survey on alcohol and relatedconditions. *Archives of general psychiatry.* 2004;61(11):1107-1115.
34. Ziedonis D, Hitsman B, Beckham JC, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine & Tobacco Research.* 2008;10(12):1691-1715.
35. Leventhal AM, Kahler CW, Ray LA, Zimmerman M. Refining the depression-nicotine dependence link: patterns of depressive symptoms in psychiatric outpatients with current, past, and no history of nicotine dependence. *Addictive behaviors.* 2009;34(3):297-303.
36. Covey LS, Manubay J, Jiang H, Nortick M, Palumbo D. Smoking cessation and inattention or hyperactivity/impulsivity: a post hoc analysis. *Nicotine & Tobacco Research.* 2008;10(12):1717-1725.
37. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry.* 2010;167(7):748-751.
38. Nutt D, Demyttenaere K, Janka Z, et al. The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. *J Psychopharmacol.* 2007;21(5):461-471.
39. Loas G. Vulnerability to depression: a model centered on anhedonia. *Journal of affective disorders.* 1996;41(1):39-53.
40. Berenbaum H, Connelly J. The effect of stress on hedonic capacity. *J Abnorm Psychol.* 1993;102(3):474-481.
41. Bogdan R, Pizzagalli DA. Acute stress reduces reward responsiveness: implications for depression. *Biol Psychiatry.* 2006;60(10):1147-1154.
42. Meehl PE. Primary and secondary hypohedonia. *Journal Of Abnormal Psychology.* 2001;110(1):188-193.
43. Lyons MJ, Toomey R, Faraone SV, Kremen WS, Yeung AS, Tsuang MT. Correlates of psychosis proneness in relatives of schizophrenic patients. *Journal Of Abnormal Psychology.* 1995;104(2):390-394.
44. Zimmerman M, McGlinchey JB, Young D, Chelminski I. Diagnosing major depressive disorder: II: is there justification for compound symptom criteria? *J Nerv Ment Dis.* 2006;194(4):235-240.
45. Leventhal AM, Piper ME, Japuntich SJ, Baker TB, Cook JW. Anhedonia, depressed mood, and smoking cessation outcome. *Journal of consulting and clinical psychology.* 2014;82(1):122.
46. Leventhal AM, Mickens L, Dunton GF, Sussman S, Riggs NR, Pentz MA. Tobacco use moderates the association between major depression and obesity. *Health Psychol.* 2010;29(5):521-528.
47. Kashdan TB, Elhai JD, Frueh BC. Anhedonia and emotional numbing in combat veterans with PTSD. *Behav Res Ther.* 2006;44(3):457-467.
48. Meinzer MC, Pettit JW, Leventhal AM, Hill RM. Explaining the covariance between attention-deficit hyperactivity disorder symptoms and depressive symptoms: the role of hedonic responsivity. *J Clin Psychol.* 2012;68(10):1111-1121.
49. Pizzagalli DA, Goetz E, Ostacher M, Iosifescu DV, Perlis RH. Euthymic patients with bipolar disorder show decreased reward learning in a probabilistic reward task. *Biological psychiatry.* 2008;64(2):162-168.
50. Hatzigiakoumis DS, Martinotti G, Di Giannantonio M, Janiri L. Anhedonia and substance dependence: clinical correlates and treatment options. *Frontiers in psychiatry.* 2011;2:10.
51. Abramovitch A, Pizzagalli DA, Reuman L, Wilhelm S. Anhedonia in obsessive-compulsive disorder: Beyond comorbid depression. *Psychiatry research.* 2014;216(2):223-229.
52. Bandelow B, Schmahl C, Falkai P, Wedekind D. Borderline personality disorder: a dysregulation of the endogenous opioid system? *Psychol Rev.* 2010;117(2):623-636.
53. Cohen AS, Najolia GM, Brown LA, Minor KS. The state-trait disjunction of anhedonia in schizophrenia: potential affective, cognitive and social-based mechanisms. *Clin Psychol Rev.* 2011;31(3):440-448.

54. Watson D, Naragon-Gainey K. On the specificity of positive emotional dysfunction in psychopathology: evidence from the mood and anxiety disorders and schizophrenia/schizotypy. *Clin Psychol Rev.* 2010;30(7):839-848.
55. Cook JW, Spring B, McChargue D, Hedeker D. Hedonic capacity, cigarette craving, and diminished positive mood. *Nicotine Tob Res.* 2004;6(1):39-47.
56. Leventhal AM, Francione Witt C, Zimmerman M. Associations between depression subtypes and substance use disorders. *Psychiatry research.* 2008;161(1):43-50.
57. Cook JW, Piper ME, Leventhal AM, Schlam TR, Fiore MC, Baker TB. Anhedonia as a component of the tobacco withdrawal syndrome. *Journal of abnormal psychology.* 2015;124(1):215.
58. Niaura R, Britt DM, Shadel WG, Goldstein M, Abrams D, Brown R. Symptoms of depression and survival experience among three samples of smokers trying to quit. *Psychology of Addictive Behaviors.* 2001;15(1):13.
59. Cook J, Spring B, McChargue D, Doran N. Effects of anhedonia on days to relapse among smokers with a history of depression: A brief report. *Nicotine & Tobacco Research.* 2010:ntq118.
60. Zvolensky MJ, Stewart SH, Vujanovic AA, Gavric D, Steeves D. Anxiety sensitivity and anxiety and depressive symptoms in the prediction of early smoking lapse and relapse during smoking cessation treatment. *Nicotine & Tobacco Research.* 2009;11(3):323-331.
61. Schnoll RA, Leone FT, Hitsman B. Symptoms of depression and smoking behaviors following treatment with transdermal nicotine patch. *Journal of addictive diseases.* 2013;32(1):46-52.
62. Schnoll RA, Hitsman B, Blazekovic S, et al. Longitudinal changes in smoking abstinence symptoms and alternative reinforcers predict long-term smoking cessation outcomes. *Drug and Alcohol Dependence.* 2016;165:245-252.
63. Balfour DJ. The neurobiology of tobacco dependence: a preclinical perspective on the role of the dopamine projections to the nucleus accumbens. *Nicotine Tob Res.* 2004;6(6):899-912.
64. Barr RS, Pizzagalli DA, Culhane MA, Goff DC, Evins AE. A Single Dose of Nicotine Enhances Reward Responsiveness in Nonsmokers: Implications for Development of Dependence. *Biol Psychiatry.* 2007.
65. Chaudhri N, Caggiula AR, Donny EC, Palmatier MI, Liu X, Sved AF. Complex interactions between nicotine and nonpharmacological stimuli reveal multiple roles for nicotine in reinforcement. *Psychopharmacology (Berl).* 2006;184(3-4):353-366.
66. Cook JW, Spring B, McChargue D. Influence of nicotine on positive affect in anhedonic smokers. *Psychopharmacology.* 2007;192(1):87-95.
67. Paterson NE, Balfour DJ, Markou A. Chronic bupropion attenuated the anhedonic component of nicotine withdrawal in rats via inhibition of dopamine reuptake in the nucleus accumbens shell. *European Journal of Neuroscience.* 2007;25(10):3099-3108.
68. Stein DJ. Depression, anhedonia, and psychomotor symptoms: the role of dopaminergic neurocircuitry. *CNS spectrums.* 2008;13(07):561-565.
69. Warner C, Shoaib M. How does bupropion work as a smoking cessation aid? *Addiction biology.* 2005;10(3):219-231.
70. Hawk LW, Ashare RL, Rhodes JD, Oliver JA, Cummings KM, Mahoney MC. Does Extended Pre Quit Bupropion Aid in Extinguishing Smoking Behavior? *Nicotine & Tobacco Research.* 2015:ntu347.
71. Slemmer JE, Martin BR, Damaj MI. Bupropion is a nicotinic antagonist. *Journal of Pharmacology and Experimental Therapeutics.* 2000;295(1):321-327.
72. Ruiz JS, Gilbert J, Fraile MG, et al. Bupropion: efficacy and safety in the treatment of depression. *Actas Esp Psiquiatr.* 2011;39(Supl 1):1-25.
73. Medicare Cf, Services M. Medicare Fee-For Service Provider Utilization & Payment Data Physician and Other Supplier Public Use File: A Methodological Overview. 2014.
74. Kahler CW, Spillane NS, Day A, et al. Positive psychotherapy for smoking cessation: Treatment development, feasibility, and preliminary results. *The journal of positive psychology.* 2013.

75. MacPherson L, Tull MT, Matusiewicz AK, et al. Randomized controlled trial of behavioral activation smoking cessation treatment for smokers with elevated depressive symptoms. *Journal of consulting and clinical psychology.* 2010;78(1):55.
76. Harvey P, Pruessner J, Czechowska Y, Lepage M. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. *Molecular psychiatry.* 2007;12(8):767-775.
77. Caggiula AR, Donny EC, Palmatier MI, Liu X, Chaudhri N, Sved AF. The role of nicotine in smoking: a dual-reinforcement model. *The motivational impact of nicotine and its role in tobacco use*: Springer; 2008:91-109.
78. Stahl SM, Pradko JF, Haight BR, Modell JG, Rockett CB, Learned-Coughlin S. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim Care Companion J Clin Psychiatry.* 2004;6(4):159-166.
79. Smith RC, Amiaz R, Si T-M, et al. Varenicline effects on smoking, cognition, and psychiatric symptoms in schizophrenia: a double-blind randomized trial. *PloS one.* 2016;11(1):e0143490.
80. Wilkes S. The use of bupropion SR in cigarette smoking cessation. *International journal of chronic obstructive pulmonary disease.* 2008;3(1):45.
81. Fava M, Rush AJ, Thase ME, et al. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion J Clin Psychiatry.* 2005;7(3):106-113.
82. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. 2014.
83. Cavazos-Rehg PA, Breslau N, Hatsukami D, et al. Smoking cessation is associated with lower rates of mood/anxiety and alcohol use disorders. *Psychological medicine.* 2014;44(12):2523-2535.
84. Emmanuel NP, Brawman-Mintzer O, Morton WA, et al. Bupropion-SR in treatment of social phobia. *Depression and anxiety.* 2000;12(2):111-113.
85. Berigan TR. The Many uses of bupropion and bupropion sustained release (SR) in adults. *Primary care companion to the Journal of clinical psychiatry.* 2002;4(1):30.
86. Stein JH, Asthana A, Smith SS, et al. Smoking cessation and the risk of diabetes mellitus and impaired fasting glucose: three-year outcomes after a quit attempt. *PloS one.* 2014;9(6):e98278.
87. Janzon E, Hedblad B, Berglund G, Engström G. Changes in blood pressure and body weight following smoking cessation in women. *Journal of internal medicine.* 2004;255(2):266-272.
88. McElroy SL. The Dual Epidemic of Tobacco Dependence and Obesity Among Those With Severe Mental Illness. *The Journal of clinical psychiatry.* 2016;77(3):327-328.
89. Thorndike AN, Achtyes ED, Cather C, et al. Weight gain and 10-year cardiovascular risk with sustained tobacco abstinence in smokers with serious mental illness: a subgroup analysis of a randomized trial. *The Journal of clinical psychiatry.* 2016;77(3):320-326.
90. Carter J, Swardfager W. Mood and metabolism: Anhedonia as a clinical target in Type 2 diabetes. *Psychoneuroendocrinology.* 2016;69:123-132.
91. Nefs G, Pouwer F, Denollet J, Kramer H, Wijnands-van Gent C, Pop V. Suboptimal glycemic control in type 2 diabetes: A key role for anhedonia? *Journal of psychiatric research.* 2012;46(4):549-554.
92. Keränen A-M, Rasinaho E, Hakko H, Savolainen M, Lindeman S. Eating behavior in obese and overweight persons with and without anhedonia. *Appetite.* 2010;55(3):726-729.
93. Pelle AJ, Pedersen SS, Szabó BM, Denollet J. Beyond Type D personality: reduced positive affect (anhedonia) predicts impaired health status in chronic heart failure. *Quality of Life Research.* 2009;18(6):689-698.
94. Davidson KW, Burg MM, Kronish IM, et al. Association of anhedonia with recurrent major adverse cardiac events and mortality 1 year after acute coronary syndrome. *Archives of general psychiatry.* 2010;67(5):480-488.

95. Denollet J, Pedersen S, Daemen J, De Jaegere P, Serruys P, Van Domburg R. Reduced positive affect (anhedonia) predicts major clinical events following implantation of coronary-artery stents. *Journal of internal medicine.* 2008;263(2):203-211.
96. Boehm JK, Kubzansky LD. The heart's content: the association between positive psychological well-being and cardiovascular health. *Psychological bulletin.* 2012;138(4):655.
97. Farley AC, Hajek P, Lycett D, Aveyard P. Interventions for preventing weight gain after smoking cessation. *The Cochrane Library.* 2012.
98. Lerman C, Berrettini W, Pinto A, et al. Changes in food reward following smoking cessation: a pharmacogenetic investigation. *Psychopharmacology.* 2004;174(4):571-577.
99. Ornellas T, Chavez B. Naltrexone SR/Bupropion SR (Contrave): A New Approach to Weight Loss in Obese Adults. *P T.* 2011;36(5):255-262.
100. Gardner E. Effects of bupropion on weight in patients intolerant to previous antidepressants. *Current therapeutic research.* 1984;35(2):188-199.
101. Gadde KM, Parker CB, Maner LG, et al. Bupropion for weight loss: an investigation of efficacy and tolerability in overweight and obese women. *Obesity Research.* 2001;9(9):544-551.
102. Jain AK, Kaplan RA, Gadde KM, et al. Bupropion SR vs. placebo for weight loss in obese patients with depressive symptoms. *Obesity research.* 2002;10(10):1049-1056.
103. Croft H, Houser T, Jamerson B. Lack of weight gain in patients taking bupropion SR: a 1-year placebo-controlled study in patients with major depression. *Obesity Research.* 2000;9:47S.
104. Jefferson JW, Pradko JF, Muir KT. Bupropion for major depressive disorder: pharmacokinetic and formulation considerations. *Clinical therapeutics.* 2005;27(11):1685-1695.
105. Schomerus G, Angermeyer MC. Special articles stigma and its impact on help-seeking for mental disorders: what do we know. *Epidemiol Psichiatr Soc.* 2008;17(1):31.
106. Lawn SJ, Pols RG, Barber JG. Smoking and quitting: a qualitative study with community-living psychiatric clients. *Social science & medicine.* 2002;54(1):93-104.
107. Dwoskin LP, Rauhut AS, King-Pospisil KA, Bardo MT. Review of the pharmacology and clinical profile of bupropion, an antidepressant and tobacco use cessation agent. *CNS drug reviews.* 2006;12(3-4):178-207.
108. Japuntich SJ, Piper ME, Leventhal AM, Bolt DM, Baker TB. The effect of five smoking cessation pharmacotherapies on smoking cessation milestones. *Journal of consulting and clinical psychology.* 2011;79(1):34.
109. Pang RD, Leventhal AM. Sex differences in negative affect and lapse behavior during acute tobacco abstinence: A laboratory study. *Experimental and clinical psychopharmacology.* 2013;21(4):269.
110. Pang RD, Zvolensky MJ, Schmidt NB, Leventhal AM. Gender differences in negative reinforcement smoking expectancies. *Nicotine & Tobacco Research.* 2014:ntu226.
111. Sussman S, Chou C-P, Pang RD, et al. Social Self-Control Is a Statistically Nonredundant Correlate of Adolescent Substance Use. *Substance use & misuse.* 2016;51(6):788-794.
112. Pang RD, Kirkpatrick MG, Goldenson NI, Guillot CR, Leventhal AM. Asians compared to Whites show increased response to d-amphetamine on select subjective and cardiovascular measures. *Pharmacology Biochemistry and Behavior.* 2016;144:73-77.
113. Goldenson NI, Pang RD, Leventhal AM. Associations between ADHD symptoms and smoking outcome expectancies in a non-clinical sample of daily cigarette smokers. *The American Journal on Addictions.* 2016;25(2):152-159.
114. Pang RD, Bello MS, Stone MD, et al. Premenstrual symptoms and smoking-related expectancies. *Addictive behaviors.* 2016;57:38-41.
115. Bello MS, Pang RD, Cropsey KL, et al. Tobacco Withdrawal Amongst African American, Hispanic, and White Smokers. *Nicotine & Tobacco Research.* 2015:ntv231.

116. Aguirre CG, Bello MS, Andrabi N, et al. Gender, Ethnicity, and Their Intersectionality in the Prediction of Smoking Outcome Expectancies in Regular Cigarette Smokers. *Behavior modification.* 2016;40(1-2):281-302.
117. Bidwell LC, Knopik VS, Audrain-McGovern J, et al. Novelty seeking as a phenotypic marker of adolescent substance use. *Substance abuse: research and treatment.* 2015;9(Suppl 1):1.
118. Guillot CR, Pang RD, Leventhal AM, Liang T, Berman ME. The association of SNCA with hazardous alcohol use is mediated by impulsivity. *Psychiatry research.* 2015;226(2-3):523-524.
119. Wolitzky-Taylor K, Guillot CR, Pang RD, et al. Examination of anxiety sensitivity and distress tolerance as transdiagnostic mechanisms linking multiple anxiety pathologies to alcohol use problems in adolescents. *Alcoholism: Clinical and Experimental Research.* 2015;39(3):532-539.
120. Pang RD, Farrahi L, Glazier S, Sussman S, Leventhal AM. Depressive symptoms, negative urgency and substance use initiation in adolescents. *Drug and alcohol dependence.* 2014;144:225-230.
121. Pang RD, Khoddam R, Guillot CR, Leventhal AM. Depression and Anxiety Symptoms Moderate the Relation Between Negative Reinforcement Smoking Outcome Expectancies and Nicotine Dependence. *Journal of studies on alcohol and drugs.* 2014;75(5):775.
122. Pang RD, Hom MS, Geary BA, et al. Relationships between trait urgency, smoking reinforcement expectancies, and nicotine dependence. *Journal of addictive diseases.* 2014;33(2):83-93.
123. Guillot CR, Pang RD, Leventhal AM. Anxiety sensitivity and negative urgency: A pathway to negative reinforcement-related smoking expectancies. *Journal of addiction medicine.* 2014;8(3):189.
124. Quinn A, Sekimura S, Pang R, Trujillo M, Kahler CW, Leventhal AM. Hostility as a predictor of affective changes during acute tobacco withdrawal. *nicotine & tobacco research.* 2014;16(3):335-342.
125. Leventhal AM, Greenberg JB, Trujillo MA, et al. Positive and negative affect as predictors of urge to smoke: temporal factors and mediational pathways. *Psychology of Addictive Behaviors.* 2013;27(1):262.
126. Sheets ES, Bujarski S, Leventhal AM, Ray LA. Emotion differentiation and intensity during acute tobacco abstinence: A comparison of heavy and light smokers. *Addictive behaviors.* 2015;47:70-73.
127. Ray LA, Bujarski S, Courtney KE, et al. The effects of naltrexone on subjective response to methamphetamine in a clinical sample: a double-blind, placebo-controlled laboratory study. *Neuropsychopharmacology.* 2015.
128. Bujarski S, Roche DJ, Lunny K, et al. The relationship between methamphetamine and alcohol use in a community sample of methamphetamine users. *Drug and alcohol dependence.* 2014;142:127-132.
129. Leventhal AM, Ray LA, Rhee SH, Unger JB. Genetic and environmental influences on the association between depressive symptom dimensions and smoking initiation among Chinese adolescent twins. *Nicotine & Tobacco Research.* 2012;14(5):559-568.
130. Ray LA, MacKillop J, Leventhal A, Hutchison KE. Catching the alcohol buzz: an examination of the latent factor structure of subjective intoxication. *Alcoholism: Clinical and Experimental Research.* 2009;33(12):2154-2161.
131. Strong DR, Kahler CW, Leventhal AM, et al. Impact of bupropion and cognitive–behavioral treatment for depression on positive affect, negative affect, and urges to smoke during cessation treatment. *Nicotine & Tobacco Research.* 2009;11(10):1142-1153.
132. Leventhal AM, Kahler CW, Ray LA, et al. Anhedonia and amotivation in psychiatric outpatients with fully remitted stimulant use disorder. *American Journal on Addictions.* 2008;17(3):218-223.
133. Ray LA, Miranda Jr R, Kahler CW, et al. Pharmacological effects of naltrexone and intravenous alcohol on craving for cigarettes among light smokers: a pilot study. *Psychopharmacology.* 2007;193(4):449-456.
134. Leventhal AM, Strong DR, Sussman S, et al. Psychiatric comorbidity in adolescent electronic and conventional cigarette use. *Journal of psychiatric research.* 2016;73:71-78.

135. Audrain-McGovern J, Leventhal AM, Strong DR. The Role of Depression in the Uptake and Maintenance of Cigarette Smoking. *International review of neurobiology.* 2015;124:209-243.
136. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *Jama.* 2015;314(7):700-707.
137. Leventhal AM, Bello MS, Unger JB, Strong DR, Kirkpatrick MG, Audrain-McGovern J. Diminished alternative reinforcement as a mechanism underlying socioeconomic disparities in adolescent substance use. *Preventive medicine.* 2015;80:75-81.
138. Leventhal AM, Unger JB, Audrain-McGovern J, Sussman S, Volk HE, Strong DR. Measuring anhedonia in adolescents: a psychometric analysis. *Journal of personality assessment.* 2015;97(5):506-514.
139. David SP, Strong DR, Leventhal AM, et al. Influence of a dopamine pathway additive genetic efficacy score on smoking cessation: results from two randomized clinical trials of bupropion. *Addiction.* 2013;108(12):2202-2211.
140. Strong DR, Leventhal AM, Evatt DP, et al. Positive reactions to tobacco predict relapse after cessation. *Journal of abnormal psychology.* 2011;120(4):999.
141. Leventhal AM, David SP, Brightman M, et al. Dopamine D4 receptor gene variation moderates the efficacy of bupropion for smoking cessation. *The pharmacogenomics journal.* 2012;12(1):86-92.
142. Kahler CW, Spillane NS, Leventhal AM, Strong DR, Brown RA, Monti PM. Hostility and smoking cessation treatment outcome in heavy social drinkers. *Psychology of Addictive Behaviors.* 2009;23(1):67.
143. Ameringer KJ, Chou C-P, Leventhal AM. Shared versus specific features of psychological symptoms and cigarettes per day: structural relations and mediation by negative-and positive-reinforcement smoking. *Journal of behavioral medicine.* 2015;38(2):224-236.
144. Leventhal AM, Mickens L, Dunton GF, Sussman S, Riggs NR, Pentz MA. Tobacco use moderates the association between major depression and obesity. *Health Psychology.* 2010;29(5):521.
145. Boutelle KN, Monreal T, Strong DR, Amir N. An open trial evaluating an attention bias modification program for overweight adults who binge eat. *Journal of behavior therapy and experimental psychiatry.* 2016;52:138-146.
146. Boutelle KN, Braden A, Douglas JM, et al. Design of the FRESH study: A randomized controlled trial of a parent-only and parent–child family-based treatment for childhood obesity. *Contemporary Clinical Trials.* 2015;45:364-370.
147. Boutelle KN, Liang J, Knatz S, et al. Design and implementation of a study evaluating extinction processes to food cues in obese children: The Intervention for Regulations of Cues Trial (iROC). *Contemporary clinical trials.* 2015;40:95-104.
148. Strong DR, David SP, Johnstone EC, Aveyard P, Murphy MF, Munafò M. Differential efficacy of nicotine replacement among overweight and obese women smokers. *Nicotine & Tobacco Research.* 2014:ntu256.
149. Courtney KE, Ghahremani DG, Ray LA. The effects of pharmacological opioid blockade on neural measures of drug cue-reactivity in humans. *Neuropsychopharmacology.* 2016.
150. Roche DJ, Ray LA, Yardley MM, King AC. Current Insights into the Mechanisms and Development of Treatments for Heavy-Drinking Cigarette Smokers. *Current addiction reports.* 2016;3(1):125-137.
151. Roche DJ, Yardley MM, Lunny KF, et al. A Pilot Study of the Safety and Initial Efficacy of Ivermectin for the Treatment of Alcohol Use Disorder. *Alcoholism: Clinical and Experimental Research.* 2016;40(6):1312-1320.
152. Ray LA, Bujarski S. Mechanisms of topiramate effects: how and for whom does it work? *Addiction biology.* 2015.
153. Roche DJ, Bujarski S, Hartwell E, Green R, Ray LA. Combined varenicline and naltrexone treatment reduces smoking topography intensity in heavy-drinking smokers. *Pharmacology Biochemistry and Behavior.* 2015;134:92-98.

154. Bujarski S, Ray LA. Negative affect is associated with alcohol, but not cigarette use in heavy drinking smokers. *Addictive behaviors.* 2014;39(12):1723-1729.
155. Li Z, Hong K, Yip I, et al. Body weight loss with phentermine alone versus phentermine and fenfluramine with very-low-calorie diet in an outpatient obesity management program: A retrospective study. *Current therapeutic research.* 2003;64(7):447-460.
156. Li Z, Hong K, Saltsman P, et al. Long-term efficacy of soy-based meal replacements vs an individualized diet plan in obese type II DM patients: relative effects on weight loss, metabolic parameters, and C-reactive protein. *European Journal of Clinical Nutrition.* 2005;59(3):411-418.
157. Hong K, Li Z, Wang H, Elashoff R, Heber D. Analysis of weight loss outcomes using VLCD in black and white overweight and obese women with and without metabolic syndrome. *International journal of obesity.* 2005;29(4):436-442.
158. Li Z, Hong K, Wong E, Maxwell M, Heber D. Weight cycling in a very low-calorie diet programme has no effect on weight loss velocity, blood pressure and serum lipid profile. *Diabetes, Obesity and Metabolism.* 2007;9(3):379-385.
159. Hong K, Herrmann K, Dybala C, Halseth A, Lam H, Foreyt J. Naltrexone/Bupropion extended release-induced weight loss is independent of nausea in subjects without diabetes. *Clinical Obesity.* 2016.
160. Ebbert JO, Hatsukami DK, Croghan IT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *JAMA.* 2014;311(2):155-163.
161. USDHHS. Clinical Guidelines and Recommendations: Treating Tobacco Use and Dependence Rockville, MD: Agency for Healthcare Research and Quality; 2008.
162. Kendrick T, El-Gohary M, Stuart B, et al. Routine use of patient reported outcome measures (PROMs) for improving treatment of common mental health disorders in adults. *The Cochrane Library.* 2016.
163. Krukowski RA, Bursac Z, Little MA, Klesges RC. The Relationship between Body Mass Index and Post-Cessation Weight Gain in the Year after Quitting Smoking: A Cross-Sectional Study. *PloS one.* 2016;11(3):e0151290.
164. Aubin H-J, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. 2012.
165. Lycett D, Munafò M, Johnstone E, Murphy M, Aveyard P. Associations between weight change over 8 years and baseline body mass index in a cohort of continuing and quitting smokers. *Addiction.* 2011;106(1):188-196.
166. Komiyama M, Wada H, Ura S, et al. Analysis of factors that determine weight gain during smoking cessation therapy. *PloS one.* 2013;8(8):e72010.
167. Kasteridis P, Yen ST. Smoking cessation and body weight: evidence from the Behavioral Risk Factor Surveillance Survey. *Health services research.* 2012;47(4):1580-1602.
168. Flegal KM. The conundrum of smoking cessation and weight gain. *Preventive medicine.* 2012;54(3):193-194.
169. Travier N, Agudo A, May AM, et al. Longitudinal changes in weight in relation to smoking cessation in participants of the EPIC-PANACEA study. *Preventive medicine.* 2012;54(3):183-192.
170. Bush TM, Levine MD, Magnusson B, et al. Impact of baseline weight on smoking cessation and weight gain in quitlines. *Annals of Behavioral Medicine.* 2014;47(2):208-217.
171. Veldheer S, Yingst J, Zhu J, Foulds J. Ten-year weight gain in smokers who quit, smokers who continued smoking and never smokers in the United States, NHANES 2003–2012. *International Journal of Obesity.* 2015;39(12):1727-1732.

172. O'Hara P, Connett JE, Lee WW, Nides M, Murray R, Wise R. Early and late weight gain following smoking cessation in the Lung Health Study. *American journal of epidemiology.* 1998;148(9):821-830.
173. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. *Journal of psychiatric research.* 2011;45(5):626-629.
174. Lee AM, Jepson C, Hoffmann E, et al. CYP2B6 genotype alters abstinence rates in a bupropion smoking cessation trial. *Biol Psychiatry.* 2007;62(6):635-641.
175. Patterson F, Schnoll RA, Wileyto EP, et al. Toward personalized therapy for smoking cessation: a randomized placebo-controlled trial of bupropion. *Clin Pharmacol Ther.* 2008;84(3):320-325.
176. Mamoun M, Bergen AW, Shieh J, Wiggins A, Brody AL. Biomarkers of Response to Smoking Cessation Pharmacotherapies: Progress to Date. *CNS Drugs.* 2015;29(5):359-369.
177. Prochaska JJ, Benowitz NL. The Past, Present, and Future of Nicotine Addiction Therapy. *Annu Rev Med.* 2016;67:467-486.
178. Wei I. Application of an urn model to the design of sequential controlled clinical trials. *Journal of the American Statistical Association.* 1978;73:559-563.
179. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict.* 1991;86(9):1119-1127.
180. Snaith R, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *The British Journal of Psychiatry.* 1995;167(1):99-103.
181. Zyban [package insert]. Research Triangle Park, NC: G laxo Smith Kline; 2016.
182. Wellbutrin X. Prescribing information. *Research Triangle Park, NC: GlaxoSmithKline.* 2010.
183. Clearing the air: Quit smoking today. Bethesda, Md: U.S. Deptartment of Health and Human Services, National Institutes of Health, National Cancer Institute; 2008.
184. Sullivan J, Sykora K, Schneiderman J, Naranjo C, Sellers E. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-AR). *British Journal of Addictions.* 1989;84:1353-1357.
185. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders - Patient edition (SCID-I/P, version 2.0). .* New York: Biometrics Research Department, New York State Psychiatric Institute.; 1995.
186. Wallenstein GV, Blaisdell-Gross B, Gajria K, et al. Development and validation of the Premenstrual Symptoms Impact Survey (PMSIS): a disease-specific quality of life assessment Tool. *Journal of Women's Health.* 2008;17(3):439-450.
187. Weinberger AH, Smith PH, Allen SS, et al. Systematic and meta-analytic review of research examining the impact of menstrual cycle phase and ovarian hormones on smoking and cessation. *Nicotine & Tobacco Research.* 2015;17(4):407-421.
188. Brown RA, Burgess ES, Sales SD, Whiteley JA, Evans DM, Miller IW. Reliability and validity of a smoking timeline follow-back interview. *Psychology of Addictive Behaviors.* 1998;12(2):101.
189. Hughes J, Hatsukami D. Errors in using tobacco withdrawal scale [Letter to the editor]. *Tobacco Control.* 1998;7(1):92-93.
190. Johnson BA, Ait-Daoud N, Roache JD. The COMBINE SAFTEE: a structured instrument for collecting adverse events adapted for clinical studies in the alcoholism field. *Journal of Studies on Alcohol, Supplement.* 2005(15):157-167.
191. Leventhal AM. The tripartite pleasure inventory: Manual and Scoring. Los Angeles, CA: University of Southern California; 2012.
192. Leventhal AM, Kahler CW. Examining socioaffective processing biases in cigarette smokers with high versus low trait hostility. *Behavioral medicine.* 2010;36(2):63-69.
193. Der-Avakian A, Barnes SA, Markou A, Pizzagalli DA. Translational assessment of reward and motivational deficits in psychiatric disorders. 2015.

194. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine & Tobacco Research.* 2001;3(1):7-16.
195. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of personality and social psychology.* 1988;54(6):1063.
196. Watson D, O'Hara MW, Simms LJ, et al. Development and validation of the Inventory of Depression and Anxiety Symptoms (IDAS). *Psychological assessment.* 2007;19(3):253.
197. Kessler RC, Adler L, Ames M, et al. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. *Psychological medicine.* 2005;35(02):245-256.
198. Anderson AL, Li S-H, Markova D, et al. Bupropion for the treatment of methamphetamine dependence in non-daily users: a randomized, double-blind, placebo-controlled trial. *Drug and alcohol dependence.* 2015;150:170-174.
199. Graham JW. Missing data analysis: making it work in the real world. *Annu Rev Psychol.* 2009;60:549-576.
200. Muthen L, Muthen B. How to use a Monte Carlo study to decide on sample size and determine power. *Struct Equ Modeling.* 2002;9(4):599-620.
201. McCarthy DE, Piasecki TM, Lawrence DL, Jorenby DE, Shiffman S, Baker TB. Psychological mediators of bupropion sustained-release treatment for smoking cessation. *Addiction.* 2008;103(9):1521-1533.
202. Japuntich SJ, Smith SS, Jorenby DE, Piper ME, Fiore MC, Baker TB. Depression predicts smoking early but not late in a quit attempt. *Nicotine & Tobacco Research.* 2007;9(6):677-686.
203. Maisto, S. A., Carey, M. P., Carey, K. B., Gordon, C. M., & Gleason, J. R. (2000). Use of the AUDIT and the DAST-10 to identify alcohol and drug use disorders among adults with a severe and persistent mental illness. *Psychological Assessment*, *12*(2), 186.