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Permalink
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Publication Date
2015-04-17

DOI
10.1007/s40263-015-0243-1

Peer reviewed
Biomarkers of Response to Smoking Cessation Pharmacotherapies: Progress to Date

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Abstract For the past 30 years, research examining predictors of successful smoking cessation treatment response has focused primarily on clinical variables, such as levels of tobacco dependence, craving, and self-efficacy. However, recent research has begun to determine biomarkers (such as genotype, nicotine and metabolite levels, and brain imaging findings) that may have utility in predicting smoking cessation. For genotype, genes associated with nicotinic acetylcholine receptors (nAChRs) and related proteins have been found to predict response to first-line medications (e.g. nicotine replacement therapy [NRT], bupropion, or varenicline) or quitting over time without a controlled treatment trial. For nicotine and metabolite levels, function of the cytochrome P450 2A6 liver enzyme, which can be assessed with the nicotine metabolite ratio or via genotype, has been found to predict response, with slow nicotine metabolizers having less severe nicotine dependence and a greater likelihood of quitting with NRT than normal metabolizers. For brain imaging, decreased activation of brain regions associated with emotion regulation and increased connectivity in emotion regulation networks, increased responsiveness to pleasant cues, and altered activation with the Stroop effect have been found in smokers who quit with the first-line medications listed above or counseling. In addition, our group recently demonstrated that lower pre-treatment brain nAChR density is associated with a greater chance of quitting smoking with NRT or placebo. Several of these studies found that specific biomarkers may provide additional information for predicting response beyond subjective symptom or rating scale measures, thereby giving an initial indication that biomarkers may, in the future, be useful for guiding smoking cessation treatment intensity, duration, and type.

Key Points

Prior research examining predictors of smoking cessation has focused on clinical variables, such as levels of tobacco dependence, craving, and self-efficacy.

Biomarkers that may have utility in predicting smoking cessation in response to specific treatments include genotypes (e.g. nicotinic acetylcholine receptor [nAChR] genes), nicotine metabolite ratios, and brain imaging findings (e.g. regional brain activation in response to cigarette cues and nAChR density).

In several studies, biomarkers have been found to provide additional predictive power beyond subjective symptoms and rating scale scores.
1 Introduction

For the past 30 years, research examining predictors of successful smoking cessation has focused primarily on clinical variables, with the most commonly studied being related to smoking, demographics, psychological symptoms, and treatment. Smoking-related factors associated with positive cessation outcomes include lower baseline craving [1, 2], severity of nicotine dependence [3–8], and number of cigarettes smoked per day [9–14]. Demographic variables shown to be helpful include higher educational level [15–18], older age [19, 20], and being married [21]. Studies have shown mixed results regarding gender as a determinant of successful cessation [9, 12, 20–24]. Numerous psychological factors have been associated with a positive response to treatment, including high baseline levels of self-efficacy [17, 18, 25–27], readiness and motivation to quit [16, 24, 28], low stress levels [29], low negative affect [30], no history of depression [31], and low anger [32]. Treatment-related factors include use of behavioral support [13, 33], adherence [34, 35], and absence of lapses during early treatment [36]. While these clinical factors have been extensively studied and utilized in the treatment of cigarette smokers for years, recent studies in the fields of genetics, nicotine metabolism, and brain imaging have begun to elucidate biomarkers associated with prediction of treatment response. To enable a narrative review of genetic, metabolic, and brain imaging biomarkers of response to smoking cessation therapies, we searched the genetics, pharmacology, pharmacogenetics, and imaging literature in the PubMed database for articles published in English from the last 20 years. Search terms included ‘clinical trial’, ‘gene’, ‘genetic analysis’, ‘smoking cessation’, ‘randomized’, ‘metabolism’, ‘plasma nicotine’, ‘cotinine’, ‘magnetic resonance imaging’, ‘spectroscopy’, ‘single photon emission computed tomography’, and ‘positron emission tomography’ for the years 1998–2015, and selected author surnames. In total, ~650 abstracts were reviewed for this paper.

2 Genetic Biomarkers

Smoking is a complex behavior with both genetic and environmental determinants. Twin studies suggest that additive genetic factors account for approximately 45–85% of variability of smoking initiation and persistence [37–40], as well as up to 75% of the variability in nicotine dependence [41–46]. Other studies suggest that 40–60% of individual differences in the ability to successfully quit may be attributable to additive genetic effects [47–49]. Meta-analyses of genome-wide association scans (GWASs) of cigarette smoking behaviors [50–55] provide genome-wide (GW) significant evidence at single nucleotide polymorphisms (SNPs) in the chr8p11.21 and chr15q25.1 nicotinic acetylcholine receptor (nAChR) gene regions, chr1q13.2 EGLN2 and CYP2A6 genes, and the 9q34.2 dopamine β-hydroxylase DBH locus. Additive score analysis of GW significant SNPs associated with cigarette consumption accounts for ~1% of the variance [56]. The aggregate effect of >500,000 common SNPs explains 10–30% of the variance of multiple nicotine and alcohol substance use/dependence traits [57]. The lower effect sizes accounted for by all GW significant SNPs, and that due to all common SNPs, compared with the estimated genetic effects from pedigree-based genetic epidemiology modeling, i.e. the ‘missing heritability’ problem [58], outlines the possible effects and limitations of pharmacogenetic biomarkers.

Most pharmacogenetic studies of prospective abstinence in randomized controlled trials (RCTs) of smoking cessation therapies (‘studies’) have focused on candidate genes (CGs) in substance dependence-relevant neurotransmitter pathways, or CGs that influence the metabolism of, or response to, nicotine, bupropion, or varenicline [59–63]. Most studies of abstinence are of a small number of selected SNPs or variable number of tandem repeat polymorphisms (VNTRs) in a single RCT. There are a smaller number of studies of two or more RCTs using association or linkage disequilibrium (LD) criteria to nominate SNPs or VNTRs into panels to interrogate CGs [61–69]. Other approaches include GW pooled allelotyping [70–72], risk score analysis based on CG or GW a priori hypotheses [73–76], or pharmacokinetic hypotheses [77–81]. Studies using CG panels and stratifying by treatment, gender, nicotine metabolism, or dependence, have identified SNPs at CHRNA2 [61], multiple nAChRs and CYP2B6 [62], SLC22A2 [63], EPB41 and CNR1 [64], DRD1 [65], and at DBH [66].

SNP or haplotype (two or more SNPs) hypothesis-driven [82–87] studies of the chr15q25.1 nAChR locus [88–93] have included analyses of one to eight RCTs. In 400 participants from two RCTs randomizing participants to bupropion or placebo treatment [94, 95], Baker et al. [88] identified a significant association by haplotype, comprised of alleles from five SNPs (rs680244, rs569207, rs16969968, rs578776, rs1051730), previously associated with increased smoking heaviness [85], with reduced abstinence from baseline to end of treatment (EOT), with no difference in association by treatment. In 270 participants from one of two RCTs treating participants with combined bupropion, nicotine replacement therapy (NRT), and cognitive behavioral therapy (CBT) to 8 weeks post-quit, then randomizing individuals to CBT and telephone counseling versus general supportive
therapy via telephone for an additional 12 weeks, Sarginson et al. [89] identified association of rs680244, previously associated with decreased nicotine dependence [86], with increased abstinence at 1 year; there were no differences in association by therapy randomization. In a meta-analysis of 1581 participants from two RCTs [96, 97] randomizing individuals to nicotine or placebo transdermal patch [96] or to two levels of behavioral support while providing all participants with nicotine patch [97], and in the RCT providing two levels of behavioral support [97], Munafò et al. [90] identified association of the principal chr15q25.1 risk SNP rs1051730 [84] with reduced abstinence at 4 weeks. In one RCT randomizing smokers to five active therapies (nicotine lozenge, nicotine patch, bupropion, nicotine patch and nicotine lozenge, bupropion and nicotine lozenge) and placebo therapy [98], Chen et al. [91] identified association of a previously defined chr15q25.1 risk haplotype (three alleles defined by rs680244 and rs16969968) [85] with reduced abstinence at EOT in smokers randomized to placebo, and a haplotype-by-treatment interaction, reflecting the lack of association of haplotype with active treatment. In a meta-analysis including 2633 individuals from eight RCTs randomizing participants to NRT, bupropion, placebo, varenicline, and combined NRT and bupropion to EOT [94, 95, 98–101], and based on the hypothesis-generating meta-analysis of Saccone et al. [82], Bergen et al. [92] identified association with 6-month abstinence in smokers carrying either of the two smoking heaviness risk SNPs rs588765 and rs1051730; smokers randomized to NRT exhibited increased cessation, and smokers randomized to placebo exhibited reduced cessation; a significant genotype-by-treatment interaction effect was observed. In an analysis of 185 participants in an RCT randomizing participants to selegiline or placebo patch [102], Sarginson et al. [93] identified association of rs3813567, previously associated with nicotine dependence [84], with reduced abstinence in smokers randomized to selegiline at week 25, but not in smokers randomized to placebo; rs3813567 carriers randomized to selegiline exhibited higher levels of craving through treatment.

Studies that have identified associations of polymorphisms at chr19q13.2 metabolic genes CYP2A6 (coding for cytochrome P450 [CYP] 2A6, the principal enzyme metabolizing nicotine [103]) and CYP2B6 (coding for CYP2B6, the principal enzyme metabolizing bupropion [104]) with abstinence have included analyses motivated by prior hypotheses based on drug metabolism studies [105–107], a CYP2A6 enzyme activity model utilizing seven CYP2A6 variants [108], or the use of LD [62] (see Sects. 3.3, 3.4).

3 Metabolic Biomarkers

3.1 Nicotine and Cotinine Levels

Nicotine and cotinine levels serve as markers of cigarette use and abstinence. Nicotine levels in plasma and urine correlate well with nicotine intake and can be measured through gas chromatography, high-performance liquid chromatography, and immunoassays [109]. Nicotine, like many other drugs, is metabolized by the liver enzyme CYP system. In humans, ~70–80 % of nicotine is converted to cotinine, largely mediated by the liver enzyme CYP2A6 [110]. Cotinine is further metabolized to its primary metabolite, trans-3'-hydroxycotinine (3HC), also by CYP2A6 [111]. Because of its long half-life (~16 h), cotinine (in plasma, urine, and saliva) is often used as a biomarker to reflect the recent use of cigarettes [112] and can also serve as verification of self-reported abstinence rates, typically for a 7-day period [109, 113].

3.2 Nicotine Metabolite Ratio

The ratio of 3HC to cotinine, termed the nicotine metabolite ratio (NMR) is used as a marker for overall nicotine clearance, and reflects individual variability in nicotine and cotinine metabolism due to variation in CYP2A6 activity, which is influenced by genetic variation and the environment [114–119]. Higher NMR indicates faster nicotine clearance and is associated with heavier smoking and lower cessation rates, possibly due to greater craving and nicotine withdrawal severity [78, 120–122]. NMR is stable in blood, plasma, and saliva at various conditions so that a single measurement of plasma NMR is reliable [123]. Other ratios of nicotine metabolites have and are being used as biomarkers of nicotine metabolism in pharmacogenetic or observational studies, e.g. the ratio of cotinine over nicotine or cotinine over the sum of nicotine and cotinine [79, 108, 124–126]. In an investigation by Patterson et al. [127], it was found that fast metabolizers of nicotine had lower quit rates with placebo, but rates were increased with bupropion treatment (10–34 %). Slow metabolizers had equal quit rates with placebo or bupropion (32 %), indicating that no further benefit was achieved with bupropion in slow metabolizers.

3.3 Cytochrome P450 (CYP) 2A6

Genetic variation that results in slower CYP2A6 activity significantly affects cigarette use, nicotine clearance, and nicotine metabolite levels [107, 115], with slow metabolizers having lower nicotine clearance and smaller NMRs, generally defined as the presence of one or two
reduced activity or null CYP2A6 alleles [108, 124], or an NMR value in the lowest quartile or lower half of the distribution [79, 107, 128, 129]. Utilizing estimates of nicotine metabolism defined by CYP2A6 genetic variation, Ho et al. [77] demonstrated that smokers of African ancestry with CYP2A6 variants associated with low enzyme activity and randomized to nicotine gum or placebo therapy, were more likely to remain abstinent than smokers with CYP2A6 variants associated with normal enzyme activity. Lerman et al. [78], who examined Caucasian smokers randomized to 6-month (‘extended’) versus 8-week (‘standard’) transdermal nicotine therapy found that smokers with CYP2A6 variants associated with reduced nicotine metabolism benefit from extended transdermal therapy more than normal metabolizers and were more likely to remain abstinent at 24 weeks. In one RCT [98], Chen et al. [79] confirmed three hypotheses linking genetically-defined slow nicotine metabolism with decreased relapse risk: (a) slow-metabolizer status alone; (b) either slow-metabolizer status or randomization to active treatment; and (c) slow-metabolizer status and randomization to NRT.

In an RCT using transdermal nicotine or nicotine nasal spray, Lerman et al. [129] showed that NMR predicted smoking abstinence (EOT and 6-month follow-up) with transdermal nicotine treatment but not nasal spray. Schnoll et al. [130] validated the NMR as a predictor of abstinence in a single-arm trial of nicotine patch treatment at 8 weeks. In a prospective NMR-stratified RCT randomizing smokers to three treatments (two active and one placebo), Lerman et al. [128] identified an NMR-by-treatment interaction at EOT and at 6 months, whereas normal metabolizers randomized to varenicline exhibited significantly increased abstinence compared with normal metabolizers randomized to nicotine patch. The efficacies of varenicline and nicotine patch were equivalent among slow metabolizers. In an RCT randomizing African ancestry light smokers to nicotine gum or placebo, Ho et al. [77] showed that smokers in the lowest NMR quartile exhibited increased abstinence overall at 26 weeks, and at both EOT and 26 weeks in females.

In addition to being a biomarker for smoking cessation efficacy on NRT, CYP2A6 slow metabolizers have been found to have other interesting associations, including smoking fewer cigarettes per day, later age of smoking onset, and smoking for a shorter duration prior to quitting [131]. In contrast to slow metabolism, rapid metabolism of nicotine may make the withdrawal process more abrupt, leading to more difficulty quitting and more severe dependence. In fact, smokers with rapid metabolizer alleles (CYP2A6*1/*1B) report more serious withdrawal symptoms during cessation [132] and have heavier smoking and lower cessation rates [120]. Furthermore, a neuroimaging study found that CYP2A6 rapid metabolizers had significantly greater responses to visual cigarette cues than slow metabolizers in the amygdala, hippocampus, striatum, insula, and cingulate cortex [133]. It is notable that smokers in these studies were not receiving smoking cessation pharmacotherapy.

Given the large number of CYP2A6 alleles that exist [106], as well as the influence of environmental factors on nicotine metabolism, the NMR may be a better biomarker than CYP2A6 alone because it includes both genetic and environmental sources of variation in nicotine metabolism and clearance [120]. Variation in treatment response among smokers with multiple genes may guide personalized smoking cessation interventions in the future.

### 3.4 CYP2B6

Although the main enzyme responsible for nicotine metabolism is CYP2A6, genetic variation at CYP2B6 leading to CYP2B6 enzyme activity differences may also be important in smoking cessation treatment response. CYP2B6 is the primary enzyme responsible for metabolism of the smoking cessation drug bupropion into its metabolite, hydroxybupropion [104]. In an RCT using bupropion and placebo [80, 81], smokers with a CYP2B6 functional polymorphism (exon 9 1459C>T) resulting in decreased CYP2B6 activity had increased relapse rates overall, and smokers randomized to bupropion with functional CYP2B6 polymorphisms resulting in increased CYP2B6 activity had increased abstinence rates. LD-motivated analyses of three RCTs randomizing smokers to varenicline, bupropion, and placebo [62] identified multiple CYP2B6 SNPs associated with abstinence at EOT and at 1 year in smokers randomized to bupropion and overall. These analyses focused on 785 SNPs from 24 genes, representing 254 LD bins (genes included nAChR subunits, additional varenicline-specific genes, and genes involved in nicotine or bupropion metabolism). One recent study identified a non-coding region in CYP2B6 (rs8109525) which may affect nicotine metabolism indirectly via altering gene splicing and allelic expression [134]. Knowledge of an individual’s CYP2B6 status may be helpful in deciding whether or not to use bupropion for smoking cessation. In a double-blind, placebo-controlled, randomized trial, it was found that higher hydroxybupropion levels (rather than bupropion levels) corresponded to better smoking cessation outcomes [135]. These findings suggested that increasing the bupropion dose for CYP2B6 slow metabolizers could improve smoking cessation outcomes.
4 Brain Imaging Biomarkers

An emerging area of research is the use of brain imaging to determine biomarkers for smoking cessation treatment response. Imaging modalities used for this research include anatomical magnetic resonance imaging (MRI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET) (see Table 1 for a summary of results). Not only do these studies relate brain structure/function to treatment response but two studies appear to demonstrate that brain biomarkers are better predictors of outcome than clinical predictors.

In one of the earliest studies in this area [136], anatomical MRIs were obtained in adult smokers prior to treatment with nicotine patch (plus reduced nicotine cigarettes [RNCs]). Smokers with higher gray matter (GM) volumes in the left putamen and right occipital lobe, and lower GM volume in bilateral hippocampi and right cuneus, were more likely to quit smoking. These results suggest that smoking abstinence is associated with higher pre-quit brain volume in regions that subserve habit learning and visual processing, and lower brain volume in regions that subserve long-term memory processes and visual information processing.

Several fMRI studies have demonstrated links between regional neural activation/deactivation in response to cigarette-related cues and quitting smoking with treatment. In an early study of this type [137], smokers underwent fMRI, during which they were presented with cigarette-related and control pictures followed by treatment with nicotine patch plus RNCs. Here, the amplitude of responses to smoking cues was larger in the thalamus than responses to control cues at baseline among future abstainers. In a second study of this type, smokers underwent fMRI, during which smoking-related pictures were presented, followed by treatment with NRT plus psychotherapy [138]. Smokers

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2-FA 2-[F-18]fluoro-A-85380, ACC anterior cingulate cortex, CBT cognitive behavioral therapy, CM contingency management, dACC dorsal anterior cingulate cortex, DLPFC dorsolateral prefrontal cortex, fMRI functional MRI, IFG inferior frontal gyrus, MRI magnetic resonance imaging, MRS magnetic resonance spectroscopy, nAChR nicotinic acetylcholine receptor, NRT nicotine replacement therapy, PCC posterior cingulate cortex, PET positron emission tomography, PFC prefrontal cortex, PMC premotor cortex, RNCs reduced nicotine cigarettes

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who did not quit had greater pre-treatment smoking-related cue activation across regions involved in sensory integration, arousal, and emotion. The authors concluded that pre-quit brain reactivity to smoking-related images is greater in smokers who do not quit, and that non-quitters have reduced pre-quit top-down control over interoceptive awareness and may be less able to regulate emotional responding to smoking-related images. Results from a third fMRI study of this type using cigarette-related and neutral cues did not find differences in regional brain activation between quitters and non-quitters who underwent treatment with varenicline [139]. However, during baseline fMRI scanning when smokers tried to resist craving, quitters demonstrated activation (compared with non-quitters) in a distributed brain network involved in alertness, learning, and memory.

In a related study using both cigarette-related cues and pleasant cues presented to smokers [140], fMRI scanning revealed that smokers who showed lower pretreatment levels of brain reactivity to pleasant cues than cigarette-related cues were less likely to be abstinent following treatment with medication plus counseling. Smokers with less response to pleasant cues also had higher levels of negative affect during the course of the quit attempt.

In addition to fMRI studies using craving and mood cues, three recent studies examined cognitive tasks, brain activity, and treatment response. For the first study [141], adolescent smokers underwent fMRI with Stroop administration, followed by treatment with CBT, contingency management, or both. Smokers with greater regional brain activation due to the Stroop effect had greater reductions in smoking. Study authors posited that adolescents with greater Stroop-related activation of cognitive control circuitry prior to behavioral therapy may be better able to decrease or quit smoking, possibly by more successfully exerting cognitive control in situations that might interfere with their quit effort. For the second study [142], smokers underwent fMRI with Stroop administration, followed by a course of treatment with varenicline. On pre-treatment fMRI scans, smokers who did not complete treatment (presumed relapers) had increased fMRI activation with the Stroop effect in the putamen and insula compared with study completers (who either quit or had large decreases in the amount smoked). In both of the preceding studies, increased activity in the insula during a cognitive control task predicted an improved likelihood of quitting. For the third study [143], smokers underwent fMRI (in abstinence and satiety) during which they performed the n-back working memory task. These sessions were followed by brief counseling and an abstinence attempt for 1 week. Study results linked abstinence-induced decreases in left dorsolateral prefrontal cortical activation and reduced suppression of posterior cingulate cortex activity to treatment outcome, thereby implicating the executive control and default mode networks, respectively, to the ability to maintain abstinence. Taken together, this series of fMRI studies has identified many regions as potentially being associated with several types of treatment response (Table 1), as well as some contradictory results and at least one negative finding. Future research could build on these initial studies by focusing on specific regional (e.g. insula or prefrontal cortical) and treatment-type hypotheses.

As for MRS studies, one study [144] examined dorsal anterior cingulate cortex (dACC) MRS glutamate (Glu/Cr) levels in smokers prior to treatment with NRT, and found that smokers who did not maintain abstinence had reduced dACC glutamate levels compared with smokers who did maintain abstinence. The authors concluded that MRS Glu/Cr ratio may be a neurobiological marker of glutamatergic dysfunction in relapse-vulnerable smokers. In contrast, a subsequent MRS study [142] did not find significant differences in baseline glutamate plus glutamine in study non-completers (presumed relapers) compared with study completers (who substantially cut down or quit smoking) with varenicline.

Our group performed two recent PET scanning studies using the radiotracer 2-FA to examine the relationship between a marker for pretreatment α4β2* nAChR density and response to smoking cessation treatment. The first of these studies [145] focused on changes in nAChR density from pre- to post-treatment with either CBT, bupropion, or placebo. In an exploratory analysis, pre-treatment markers for nAChR density had trend-level indications that lower nAChR density in three brain regions studied was associated with a greater likelihood of quitting. In the second study [146], using the same PET method, a relatively large sample of smokers underwent double-blind, placebo-controlled treatment with nicotine patch. Smokers with lower pretreatment nAChR density (a possible marker of less severe nAChR upregulation) across all brain regions studied were more likely to quit smoking, regardless of treatment group. Furthermore, pretreatment average nAChR densities provided additional predictive power for the likelihood of quitting beyond self-report measures. While it is recognized that the costly, time-consuming PET procedure used by our group is not likely to be used clinically, simpler methods for examining α4β2* nAChR upregulation could be tested and applied in the future to help determine which smokers may need more intensive and/or lengthier treatment.

Most of the brain imaging studies reviewed in this section were described as preliminary or pilot work; however, some intriguing findings were reported that are worthy of future research. Novel findings include decreased activation of brain regions associated with emotion regulation and increased connectivity in emotion regulation networks,
increased responsiveness to pleasant cues, and altered activation with the Stroop effect in smokers who quit. Furthermore, our finding of lower pre-treatment nAChR density in smokers who quit was indicated preliminarily in one study and found to be significant in a second, indicating that smokers with greater objective evidence of brain nicotine exposure have more difficulty quitting than smokers with evidence for less nicotine exposure.

5 Conclusions

While clinical predictors of smoking cessation treatment response have been extensively studied, emerging evidence suggests that genetic, metabolic, and brain imaging biomarkers are useful in predicting response. Specifically, genes for nAChRs (and related proteins), determinants of nicotine metabolism, and brain imaging findings related to cigarette cue responses and nAChR levels have been found to predict response. Furthermore, several of these studies found that specific biomarkers may provide additional information for predicting response beyond subjective symptom or rating scale measures [136, 138, 143, 146]. Current research is focusing on clinical applicability of NMR [147], which is likely the most robust biomarker of nicotine metabolism, and brain imaging findings related to cigarette cue responses and nAChR levels have been found to predict response. However, in future, influence treatment intensity and duration, and perhaps also guide choice of treatment.

Acknowledgments

This work was supported by grants from the National Institute on Drug Abuse (R01 DA20872), the Department of Veterans Affairs, Office of Research and Development (CSRI&D Merit Review Award 101 CX000412), and the Tobacco-Related Disease Research Program (#23XT-0002) to Arthur L. Brody, and a grant from the National Institute on Drug Abuse (R21 DA33813) to Andrew W. Bergen. Michael Mamoun, Andrew W. Bergen, Arthur L. Brody, Jennifer Shieh and Anna Wiggins report no conflicts of interest.

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