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Prefrontal Cognitive Dysfunction is Associated with Tobacco Dependence Treatment Failure in Smokers with Schizophrenia

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Abstract

Background—Patients with schizophrenia have higher rates of smoking (58–88%) than in the general population (~22%), and are more refractory to smoking cessation. These patients also exhibit numerous neurocognitive deficits, some of which may be ameliorated by cigarette smoking. The neurocognitive benefits derived from nicotine may, in turn, contribute to elevated rates of smoking and smoking persistence in schizophrenia. The present study examined the relationship between neurocognitive function and smoking cessation in schizophrenia.

Methods—Treatment-seeking smokers with schizophrenia (N = 58) participated in a 10-week placebo-controlled trial of sustained-release (SR) bupropion plus transdermal nicotine patch. Neuropsychological performance was evaluated in a subset of patients (n = 31), prior to pharmacological treatment, using a neurocognitive battery.

Results—Subjects were compared as a function of endpoint smoking status (Quit versus Not Quit, assessed by end of trial 7-day point prevalence abstinence, confirmed by CO level (<10 ppm) on

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Contributors

Author Tony George designed the study and wrote the protocol. Authors Taryn Allen, Jennifer Vessicchio and Kristi Sacco managed the study. Authors Andrea Weinberger and Taryn Moss undertook the statistical analysis, and author Taryn Moss and Tony George wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

Dr. George reports that he is a consultant to and on the Speaker's Bureau of Pfizer, Eli Lilly, Janssen-Ortho and Prempharm, and has grant support from Pfizer, Targacept, Sepracor and Sanofi.

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demographic traits, smoking, and clinical outcomes. While there were no significant baseline differences between quitters and non-quitters, non-quitters exhibited significantly greater deficits in performance on TMT-B ($p=0.01$) and on Digit Span backwards ($p=0.04$) compared to quitters. No associations were found between quit status and performance on other neuropsychological measures.

Conclusions—Our findings extend results of previous studies which suggest deficits in frontal executive function are associated with smoking cessation failure in schizophrenia. This may have implications for the development of tailored smoking cessation treatments in this population.

Keywords

Smoking cessation; Schizophrenia; Cognition; Neuropsychology; Clinical Trial; Pharmacotherapy

1. Introduction

Schizophrenia is a serious and persistent mental illness, and persons with this illness have elevated rates of smoking (58–88%) when compared to the general population (~22%) (George et al., 2008; Kalman et al., 2005; Weinberger et al., 2007a). This disorder has been linked to a variety of neurocognitive deficits, which may be ameliorated through cigarette smoking (Dolan et al., 2004; George et al., 2008; George et al., 2002a; Smith et al., 2002). The prefrontal cortex (PFC) mediates several cognitive domains, including executive function (Dolan et al., 2004; George et al., 2008; Morice and Delahunty, 1996; Sacco et al., 2005) and spatial working memory (Dolan et al., 2004; Keefe et al., 1995; Park and Holzman, 1992). PFC-related cognitive deficits have been suggested to be mediated by cortical dopamine (DA) hypofunction (Knable and Weinberger, 1997). Additionally, persons with schizophrenia have a reduction in gray matter volume in the PFC region (Dolan et al., 2004; Gur et al., 2000), which suggests they suffer from both prefrontal cortical structural and neurochemical abnormalities. Interestingly, in a study involving non-human primates (Tsukada et al., 2005), acute intravenous administration of nicotine was found to normalize PFC DA levels and improve spatial working memory (George, 2007).

Nicotine derived from cigarette smoking reduces haloperidol-induced working memory and attentional deficits (Dolan et al., 2004; Freedman et al., 1997; Levin et al., 1996). Dolan and colleagues (2004) demonstrated that among participants with schizophrenia, those with greater deficits in visuospatial working memory (VSWM) and Wisconsin Card Sorting Task (WCST) (Heaton et al., 1993) performance, were significantly less likely to quit smoking. Previous findings have suggested that smoking abstinence can exacerbate VSWM deficits in smokers with schizophrenia but not control comparisons (George et al., 2002a). VSWM has been shown to be partially mediated by DA function in the PFC. The pathophysiology of schizophrenia may be mediated, in part, by dysregulation of mesolimbic and mesocortical DA pathways (Ziedonis and George, 1997). A plausible explanation for the high smoking rates in this population may be related to remediation of DA hypofunction in the PFC and associated cognitive deficits by nicotine administration (Dolan et al., 2004; George et al., 2002a). The goal of the present study was to investigate whether neuropsychological function was associated with treatment outcomes in smokers diagnosed with schizophrenia, with the specific hypothesis that deficits in PFC cognitive function may be associated with smoking cessation failure in these patients.

It is a concern of medical professionals that smokers with schizophrenia face greater difficulty with smoking cessation, as demonstrated by their lower endpoint abstinence rates in smoking cessation trials when compared with non-psychiatric smokers (Addington et al., 1998; Evins et al., 2001; George et al., 2002a; Weiner et al., 2001). Given the high risk for the development of smoking-related diseases, it is imperative to create enhanced methods for smoking cessation

among smokers with schizophrenia (Dolan et al., 2004; George et al., 2008; Weinberger et al., 2007b). A better understanding of the association between neurocognitive function and nicotine addiction in schizophrenia may offer insight into novel ways for treating nicotine addiction in schizophrenia.

Accordingly, the goal of the present study was to evaluate the relationship between neurocognitive function and smoking cessation treatment outcomes (e.g., quitting versus not quitting smoking) in smokers with schizophrenia. It was hypothesized that PFC-related neuropsychological function would be associated with treatment outcomes in those diagnosed with schizophrenia as they have deficits in PFC mediated cognitive functions as compared to non-psychiatric controls. In particular, we predicted that inferior performance on tests of PFC-dependent executive function and VSWM, would be associated with smoking cessation treatment failure in individuals with schizophrenia.

2. Methods

2.1 Participants

Treatment-seeking smokers with schizophrenia (N= 58) participated in a 10-week double-blind, randomized placebo-controlled trial of sustained-release (SR) bupropion plus transdermal nicotine patch (George et al., 2008). Neuropsychological performance was evaluated in a subset of patients (n=31) prior to study randomization and pharmacological treatment. Smokers with schizophrenia were recruited through advertisements and clinicians referrals at the Connecticut Mental Health Center in New Haven, CT USA.

All psychiatric diagnoses were established using the SCID-I for DSM-IV, administered by trained research staff (JCV and KAS). Participants were included in the studies if they had a primary diagnosis of schizophrenia or schizoaffective disorder, and all subjects were clinically stable and sustained on a stable dose of an antipsychotic drug (typical or atypical) for at least one month prior to enrollment. Subjects were also administered the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987) in order to measure level of psychiatric symptomatology, and the Beck Depression Inventory (BDI), both during screening and again on the day of the cognitive assessments. All subjects were required to have a Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al., 1991) score of ≥ 5 , self-reported smoking of ≥ 10 cigarettes per day, an expired carbon monoxide (CO) level ≥ 10 ppm, and a plasma cotinine level ≥ 150 ng/ml at study baseline. In addition, a full-scale IQ estimate was obtained from the Shipley Institute of Living Scale. While subjects were not excluded on the basis of their IQ scores, it was measured in order to better understand the sample, consistent with previous neuropsychological research (Sacco et al., 2006). Participants were excluded if they met criteria for a substance use disorder (excluding nicotine and caffeine) in the three months prior to study participation or reported any contraindications to the study medications.

2.2 Determination of smoking abstinence

Smoking abstinence (7-day point prevalence) was defined by an absence of self-reported cigarette use in the seven days prior to, and including the day of assessment. These verbal reports of smoking abstinence were biologically confirmed weekly by CO < 10 ppm (George et al., 2002a). Those who dropped out of the study prior to completion were classified as non-quitters.

2.3 Neuropsychological assessment procedures

A comprehensive neuropsychological battery was administered at the baseline assessment in order to survey a broad range of neurocognitive processes (verbal memory, mental flexibility, adaptability to feedback, cognitive switching, spatial and non-spatial working memory,

attention and concentration, decision-making and psychomotor performance), with an emphasis on PFC function. The computerized neuropsychological tests administered include the Continuous Performance Test – Second Edition (CPT-II v.5) to measure attention, a test of Visuospatial Working Memory (VSWM), the Wisconsin Card Sorting Test (WCST) to assess concept-formation, problem-solving and cognitive flexibility (Berman et al., 1995; Yip et al., 2009), and the Iowa Gambling Test (IGT) to measure decision-making. Pen and paper tasks included The California Verbal Learning Test – Second Edition (CVLT-II) to assess verbal memory, the Digit Span (DS) of the WAIS-III for working memory, and the Trail Making Test (TMT) Parts A (processing speed) and B (cognitive switching). This neurocognitive battery took approximately two hours to complete. All participants smoked ad lib during the neuropsychological testing session (e.g., they were provided with structured cigarette breaks as well as additional cigarette breaks as requested), and CO levels were assessed prior to each neuropsychological testing session to verify current smoking status. The procedures for the computerized VSWM was adapted from previously published “pen-and-paper” versions of this test (Hepp et al., 1996; Keefe et al., 1995), using PsyScope version 1.1 on a Macintosh computer. CPT-II and the WCST were administered on a PC, using commercially available software (from Multi-Heath Systems, Toronto, Canada and Psychological Assessment Resources, Lutz, FL, respectively). For all computerized neuropsychological tests, subjects sat in front of the computer with a viewing distance of 60 cm, and a visual field of ~ 50°. All other neuropsychological tests (Digit Span, TMT, and CVLT-II) were administered by trained research staff according to standardized procedures.

2.3.1 Attention/Vigilance

Continuous Performance Task – Second Edition (CPT-II) (Connors, 1995): The CPT-II is a test designed to measure sustained attention, concentration and impulsivity. With this task participants are required to monitor a continuous presentation of stimuli for a specific target (“X”) in a string of consecutively presented letters on the computer screen in a rapid manner (Lezak, 1995). Common measures reported include reaction time, % Hit Rate (the primary measure of sustained attention), % Omissions, % Commissions, Reaction Time Response Variability, and Attentional Index (d’). The CPT task is commonly employed in schizophrenia research (Hazlett et al., 2008; Sacco et al., 2005; Salgado-Pineda et al., 2003).

2.3.2 Speed of Processing

Trail Making Test (TMT), Part A (Army Individual Test Battery, 1944): The Trail Making Test is given as a paper-and-pencil administration in two parts, Part A and Part B. The TMT is commonly used in neuropsychological research involving individuals with schizophrenia, and abnormal performance has been recurrently documented (Perianez et al., 2007). Part A involves drawing lines to connect consecutively numbered circles and measures visual-motor processing speed.

2.3.3 Executive Function

Trail Making Test (TMT), Part B (Army Individual Test Battery, 1944): The TMT Part B involves alternating between a number and lettered sequence requiring the subject to cognitively shift set, assessing aspects of executive functioning including shifting set and cognitive flexibility. Executive functions are controlled by brain systems, which involve the prefrontal cortex and include the planning, sequencing or temporal elements of behaviour (Wolwer and Gaebel, 2002).

Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993): The WCST is a widely used task designed to assess various executive functions, including cognitive flexibility, and use of environmental feedback to modify cognitive sets (Aharonovich et al., 2008; Dolan et al.,

2004). Outcome measures include number of categories completed, percent total errors, percent perseverative errors, percent non-perseverative errors, and number of trials to complete first category. Performance on this task has been linked with activation of the dorsolateral prefrontal cortex (Egan et al., 2001).

Iowa Gambling Test (Bechara et al., 1994): The Iowa Gambling Test task is designed to simulate real-life decision making. Decision-making is a executive cognitive process that has been suggested to play a role in smoking cessation treatment outcome (Krishnan-Sarin et al., 2007). In this task participants are shown four decks of cards on a computer screen. They are instructed to choose a card and told they will be granted some game money. They are warned that occasionally choosing a card causes them to lose money. The goal of the game is to win money. Among the cards, some decks are “bad decks”, and other decks are “good decks”, as some will lead to losses over the long run, and others will lead to gains. The decks differ from each other in the amount of trials over which the losses are distributed. Previous research has suggested that individuals with schizophrenia are significantly impaired on IGT in comparison to healthy controls, as they earn significantly lower scores and make more disadvantageous picks (Beninger et al., 2003; Kester et al., 2006).

2.3.4 Working Memory

Visuospatial Working Memory (VSWM): Spatial working memory depends, in part, on prefrontal cortical DA systems; cortical DA hypofunction and hippocampal deficits in schizophrenia appears to be responsible for deficits in spatial working memory in individuals with schizophrenia (Castner et al., 2000; George et al., 2002b; Williams and Goldman-Rakic, 1995). This task is a delayed-response spatial working memory task, which is commonly used to assess working memory (George et al., 2002b; Sacco et al., 2005), and was adapted for computer use in Dr. George’s laboratory (George et al., 2002a; Sacco et al., 2008; Sacco et al., 2006; Sacco et al., 2005). The VSWM involves the subject visualizing an object at a particular location on the computer screen (Screen 1), then seeing a “distracter task” screen which entails a sham performance task (“tic-tac-toe”; Screen 2) appearing for variable fixed time intervals (e.g., delay condition of 30 or 60 seconds). This is followed by a final screen that prompts the subject to identify exactly where the object was located on the first screen (Screen 3). VSWM performance results are reported as the averaged “distance from target” in cm for the 16 trials at each delay condition, with higher scores indicating more impaired VSWM performance (Keefe et al., 1995).

Digit Span of WAIS-III (Wechsler, 1997): Digit Span (DS) is a subtest of the Wechsler intelligence and memory batteries, and is often used in schizophrenia research (Park and Holzman, 1992; Stefansson and Jonsdottir, 1996). This subtest has two parts: forward and backward. Subjects are read a series of numbers and are required to repeat the digit sequence back to the examiner either exactly as stated (forward) or in reversed order (backward). Forward is thought to measure simple aural attention, while backward requires storage of information for mental manipulation of the digits and is considered a measure of working memory (Lezak, 1995).

2.3.5 Verbal Memory

California Verbal Learning Test – Second Edition (CVLT-II) (Delis et al., 2000): The CVLT-II is a verbal learning test assessing encoding, immediate and delayed recall and recognition of new verbal information with the use of a sixteen-item list. Items are categorized into four semantic groups of four words each presented in randomized order. Subjects are presented this list (List A) five times, recalling the items after each presentation. They are then administered an interference list (List B) that they are required to recall followed by an additional recall of List A, measuring proactive and retroactive interference. Subjects are provided categorical

cues after the interference trial, and after a 30-minute delay, are asked to recall List A. There is also a recognition/forced-choice discrimination trial. The CVLT-II is a widely used measure of verbal learning and memory and has been used frequently in schizophrenia studies (Hawkins and Wexler, 1999; Heinrichs and Zakzanis, 1998; Saykin et al., 1991).

2.4 Statistical Analyses

Endpoint smoking status (Quitters versus Non-Quitters) was determined by 7-day point prevalence abstinence during the last week of the trial, confirmed by CO level <10 ppm. Comparisons of demographic and clinical characteristics, and neuropsychological test performance between the two quit status groups (Quitters versus Non-Quitters) were performed by Independent samples t-tests. Logistic regression analyses were used to examine demographic variables (level of education, IQ, and nicotine dependence) associated with smoking abstinence. A forward Wald model was used entering the demographic variables in one step. The Nagelkerke R^2 is reported for the logistic regression results. Statistical analyses were performed using SPSS v.15.0 software for PC. Statistical tests were two-tailed and differences were considered significant when $p < 0.05$.

3. Results

3.1 Demographics and clinical characteristics of sample (Table 1)

Thirty-one smokers with schizophrenia (74% male) completed the neurocognitive assessments. At trial endpoint, 10 participants (60% male) were confirmed to be abstinent from smoking and 21 participants (81% male) were still smoking. See Table 1 for a comparison of demographic and clinical characteristics by Quit status. There were no differences between Quitters and Non-Quitters in terms of age, sex, or race composition ($p > 0.05$). Participants who successfully quit smoking smoked fewer cigarettes per day and had significantly lower levels of nicotine dependence at baseline when compared with non-quitters. In addition, Quitters had higher IQ levels and reported more years of education than Non-Quitters. The PANSS scores indicated a moderate level of psychotic symptoms, and both PANSS and depression scores were similar across groups. The trial participants who did not participate in the neurocognitive testing ($n=27$) did not significantly differ on demographic and clinical characteristics from those that did participate (data not shown).

3.2 Relationship of baseline neuropsychological test performance to quit status at trial endpoint (Table 2)

Non-Quitters exhibited significantly greater deficits in performance on TMT-B ($p = 0.02$) and on Digit Span backwards ($p = 0.04$) compared to Quitters. No other significant associations were found between quit status and performance on other neuropsychological measures, however, IGT showed a trend towards significance ($p < 0.09$).

3.3 Demographic and smoking predictors of endpoint smoking status

A logistic regression analysis taking into account baseline differences (estimated IQ score, years of education, and FTND) between quitters ($n = 10$) and non-quitters ($n = 21$) revealed that FTND [Wald (1) = 4.85, $p < .05$] was a significant predictor of smoking cessation [full model Nagelkerke $R^2 = 0.32$]. Participants with higher levels of nicotine dependence were less likely to be abstinent from smoking at the end of the trial. No other demographic or smoking variables that were entered into the model were found to significantly predict smoking cessation.

4. Discussion

4.1 Specific neurological deficits are associated with smoking cessation treatment failure in schizophrenics

The results of the present study suggest that selected pre-intervention neuropsychological deficits are associated with smoking cessation treatment failure in smokers with schizophrenia. This was evident in a subset of smokers with schizophrenia ($n = 31$) that participated in a tobacco treatment intervention with the combination of transdermal nicotine patch and sustained-release bupropion (George et al., 2008). The majority of subjects achieving end of trial smoking abstinence were treated with this combination as compared to those in the control intervention (active patch plus placebo bupropion; Table 1). Interestingly, the tasks that were significantly associated with successful treatment outcome included Trails B and Digit Span (backwards), two general measures of frontal executive cognitive function (Lezak, 1995). There was a trend indicating that deficits on the Iowa Gambling Task (IGT; $p = 0.09$), a measure of decision-making function linked to orbitofrontal cortical function (Bechara et al., 1994), were associated with smoking treatment failure in smokers with schizophrenia.

Education has been identified as a socio-demographic predictor of smoking cessation (Barbeau et al., 2004; Wetter et al., 2005). Level of education and IQ are linked and we found these two demographic factors to be significantly correlated in this sample ($r = .41$, $p < .05$). Moreover, FTND was also included in the logistic regression since level of nicotine dependence is related to increased difficulty with cessation (Augustson et al., 2008; Chandola et al., 2004). These factors (education, IQ and FTND score) were significantly different between quitters and non-quitters in the present sample of smokers with schizophrenia. However, we did not control for these between group differences in analyzing the observed neuropsychological differences (TMT-B and DS-B) between groups as a function of trial endpoint smoking status since these are likely to be independent predictors of treatment outcome not directly associated with a diagnosis of schizophrenia or its related neurocognitive dysfunction.

4.2 Comparison with Previous Studies

Our findings extend results of previous studies that suggest prefrontal executive deficits are associated with smoking cessation failure in treatment-seeking smokers with schizophrenia. In contrast, Dolan and colleagues (2004) found subjects who had greater deficits in VSWM and WCST performance were significantly less likely to quit smoking. Although the present study did not replicate these specific findings, possibly due to methodological differences in the administration of the VSWM and WCST in the present studies as compared to that by Dolan et al. (2004), both studies indicate frontal executive and working memory deficits are associated with smoking cessation treatment failure.

Other research has reported similar findings with regards to cognitive functioning and cessation ability in other drug-dependence disorders. For example, Aharonovich et al. (2006) assessed cognitive performance in cocaine-dependent patients ($n = 56$) prior to enrollment in an outpatient cognitive behavioural trial. Those who failed to complete treatment had poorer cognitive functioning as evidenced by significantly lower scores on the MicroCog neurocognitive battery. Similarly to the present study, Aharonovich et al. did not find a significant difference between abstainers vs. non-abstainers on the WCST.

More recently, Aharonovich and colleagues (2008) investigated cognitive functioning at treatment entry and its relation to retention and drug use outcome in marijuana-dependent patients ($n = 20$). They found that cognitive functioning was not associated with abstinence among these individuals. However, those who failed to complete the treatment scored significantly lower on measures of abstract reasoning and processing accuracy. Both of the

aforementioned studies (Aharonovich et al., 2008; Aharonovich et al., 2006) suggest that cognitive impairments negatively affect response to treatment for substance dependence, and are consistent with the results of the present investigation.

4.3 Implications for Treatment of Tobacco Dependence in Schizophrenia

Smoking cessation failure was associated with deficits in frontal-executive function among treatment-seeking smokers with schizophrenia. This suggests that targeting prefrontal deficits through pharmacological (e.g. medications which improve prefrontal dopaminergic function (Sacco et al., 2008) or behavioral (e.g. cognitive remediation therapies) interventions might improve smoking cessation outcomes among individuals with schizophrenia. Such an approach may be important for the development of tailored smoking cessation treatments in this population. This may have important public health implications for smokers with serious mental illness like schizophrenia, who have higher rates of smoking compared to the general population, greater difficulty with smoking cessation, and the high probability of morbidity and mortality as a result of smoking-related medical conditions (Kalman et al., 2005).

4.4 Limitation of the present study

It is important to note that there were specific limitations to the present study. In particular, the sample size here was relatively small, as only a subset of subjects (31/58) entering the parent clinical trial (George et al., 2008) were assessed on the neurocognitive battery. Therefore, these findings should be considered preliminary. Also, our findings on VSWM and WCST did not confirm the results of our previous studies (Dolan et al. (2004)), which may be related to methodological differences between the two studies.

4.5. Conclusions

The findings from the present study suggest that individuals with schizophrenia who have relatively robust baseline deficits in PFC-related neuropsychological test performance may experience more difficulty quitting smoking. Neuropsychological benefits that may be derived from nicotine administration via cigarette smoking may lead patients to continue this habit (e.g. George et al., 2002; Smith et al., 2002; Sacco et al., 2005; George et al., 2006). As a result, it may be beneficial to develop smoking cessation interventions toward remediation of PFC-related neuropsychological deficits in schizophrenia.

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Table 1
Demographic and Clinical Characteristics of Quitters and Non-Quitters with Schizophrenia

	Quitters (n = 10)	Non-Quitters (n = 21)	p-value
Age	39.8 ± 7.9	40.4 ± 7.4	p = 0.84
Sex	6 M/4 F	17 M/4 F	p = 0.38
Race	5 W/4 AA/1 H	8 W/12 AA/1 H	p = 0.63
Education	12.4 ± 1.9	11.1 ± 2.3	p = 0.15
Estimated Full-Scale IQ	90 ± 11.7	81.86 ± 12.5	p = 0.08
# Cigs per day	11.4 ± 15.1	24.2 ± 10.6	p < 0.01*
Baseline Carbon Monoxide Level (ppm)	10.6 ± 10.5	28.6 ± 17.2	p < 0.02*
End-of-Trial CO Level (ppm)	1.4 ± 0.8	18.1 ± 9.1	p < 0.02*
FTND	3.4 ± 3.7	6.95 ± 1.6	p < 0.01*
Plasma Cotinine (ng/mL)	386 ± 252	474 ± 252	p = 0.39
BDI	11.1 ± 8.6	8.81 ± 9.7	p = 0.53
BPRS	40 ± 6.2	35.8 ± 7.5	p = 0.30
PANSS Positive	15 ± 3.4	13.57 ± 3.6	p = 0.30
PANSS Negative	15 ± 2.6	15.6 ± 2.8	p = 0.56
PANSS General	31.7 ± 3.8	29.19 ± 5.7	p = 0.22
PANSS Total	62.6 ± 8.5	57.9 ± 10.33	p = 0.33
Medication	8 Atypical 2 Clozapine 4 Risperdone 2 Olanzapine 1 Quetiapine 1 Thiothixene	16 Atypical/3 Typical 4 Clozapine 7 Risperdone 7 Olanzapine 3 Fluphenazine	p = 0.27
Bupropion versus Placebo	8 Bupropion/2 Placebo	11 Bupropion/10 Placebo	p = .15
Chlorpromazine (CPZ) Equivalents (mg/day)	474.9 ± 336.0	517.4 ± 316.5	p = 0.76

Table 2

Baseline Neuropsychological Performance as a Function of Trial Endpoint Quitter and Non-Quitter Status in Treatment-Seeking Smokers with Schizophrenia

	Quitters (n = 10)	Non-Quitters (n = 21)	p-value
CPT Hit Rate (%)	98.4 ± 94 (96.6 – 100)	97.8 ± 2.1 (91.4 – 100)	p = 0.32
CPT Attentional Index	2.9 ± 85 (1.52 – 4.49)	2.3 ± 1.2 (–1.21 – 4.04)	p = 0.23
VSWM 30-Second Delay	1.8 ± 1.2 (.73 – 4.47)	2.1 ± 0.87 (.67 – 3.99)	p = 0.46
VSWM 60-Second Delay	1.9 ± 1.7 (.70 – 5.86)	2.2 ± .92 (1.05 – 4.79)	p = 0.46
WCST % Preservative Errors	19.6 ± 13.6 (6 – 43)	16.9 ± 9.8 (5 – 41)	p = 0.53
WCST Categories Completed	3.3 ± 2.6 (0 – 6)	2.9 ± 2.07 (0 – 6)	p = 0.65
TMT Part A	32 ± 16.4 (17 – 61)	40.9 ± 15.4 (20 – 77)	p = 0.15
TMT Part B	69.6 ± 23.6 (40 – 105)	121.2 ± 51.2 (57 – 240)	p = 0.01*
Digit Span Forwards	8.8 ± 1.7 (7 – 13)	8.8 ± 2.5 (4 – 13)	p = 0.99
Digit Span Backwards	6.2 ± 1.5 (4 – 8)	4.9 ± 1.7 (2 – 9)	p = 0.04*
Iowa Gambling Test	12.8 ± 14.9 (–8 – 42)	–1.32 ± 22.8 (–52 – 40)	p = 0.09
CVLT	35.8 ± 10.42 (21 – 55)	34.9 ± 11.92 (16 – 69)	p = .84