BIOBEHAVIORAL NICOTINE DEPENDENCE
IN PERSONS WITH SCHIZOPHRENIA

DISSEMINATION
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By
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ABSTRACT

Tobacco use is the leading cause of preventable death in the United States. While the prevalence of smoking by adults in the United States has decreased, those with mental illness are estimated to consume nearly one-half of all cigarettes smoked in the United States. Persons with schizophrenia have the highest reported smoking prevalence, reaching as high as 83%. In addition, those with schizophrenia are more likely to be heavy smokers.

Schizophrenia is a debilitating disease associated with varied symptomology, including impaired cognitive functioning. The ability to study factors that influence health such as nicotine dependence in persons with schizophrenia has been challenged by this impaired functioning. Persons with schizophrenia have variable performance on decision making capacity scores. They perform lower than subjects without mental illness, but higher than those with dementia. Recent strategies and educational interventions regarding informed consent have enhanced the ability of those with schizophrenia to recall, understand, and provide informed consent. These techniques were used in the current study and are reported in the first manuscript.

Persons with schizophrenia use nicotine to self-medicate for symptoms of the disease process and for side effects of their antipsychotic medications. The use of
biological markers to assess nicotine dependence in this population has relied predominantly upon carbon monoxide levels with relatively few studies using nicotine and cotinine concentrations. Limited smoking-related research in persons with schizophrenia indicated a need to further nicotine dependence according to the type of antipsychotic medication category labeled as atypical and typical antipsychotics. Persons on atypical antipsychotics have shown lower levels of nicotine dependence with corresponding lower levels of carbon monoxide. The second manuscript focuses on the extant research on pharmacological smoking cessation interventions in persons with schizophrenia.

This dissertation study recruited smokers with schizophrenia prescribed either atypical or typical antipsychotic medications to address the research aims of comparing the two groups on atypical and typical antipsychotic medications at baseline and to determine if there were changes either within or between the groups over time during eight weeks of bupropion use. Individuals were enrolled after correctly completing all items of the comprehension questionnaire related to the study’s informed consent. Each participant was prescribed bupropion sustained release tablets for a period of eight weeks. Bupropion is classified as an effective smoking cessation pharmacotherapy. Four visits were scheduled: baseline, and at two, four, and eight weeks. This study incorporated multiple measures to examine the biobehavioral characteristics of smoking in person with schizophrenia. Measurements included smoking topography (the unique way an individual puffs a cigarette), carbon monoxide in exhaled air, plasma nicotine, and plasma cotinine concentrations. To
assess for safety and side effects of bupropion, standardized tests of Montgomery-Asberg Depression Rating Scale and Positive and Negative Symptom Scale for Schizophrenia were conducted at baseline and at four and eight weeks. The Abnormal Involuntary Movement Scale was completed at baseline and eight weeks.

Our study found no significant differences between the two groups in either smoking topography or biological measures at baseline. When comparing data over the four visits, changes were noted in the way that the cigarette was smoked in both groups. There were significant within subject differences over time in both groups on interpuff interval, flow rate, and peak flow. Interpuff intervals shortened over time in the atypical medication group; flow rate and peak flow increased over time in both groups. Carbon monoxide boost pre to post-cigarette was significantly different over time between groups with a decrease in those on atypical medications, but remaining the same in those on typical medications. Significant within group changes occurred over time on both post-cigarette nicotine and cotinine levels. Both groups decreased in post-cigarette nicotine and cotinine concentrations indicating a decrease in cigarette consumption.

The medication bupropion was well tolerated by the participants based upon the use of standardized instruments. This study found that use of bupropion could reduce smoke constituent exposure and affect smoking patterns in those who were not interested in cessation nor enrolled in a lengthy smoking cessation program. A long-term harm reduction in tobacco consumption may be a second best goal for those who are unsuccessful at cessation or do not wish to quit smoking.
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ABBREVIATIONS

DSM=Diagnostic and Statistical Manual of Mental Disorders
GED=General Educational Development
min=minutes
ml/sec=milliliter per second
mm=millimeter
ng/ml=nanograms per milliliter
ppm=parts per million
sec=seconds
CHAPTER 1

SPECIAL CONSIDERATIONS IN CONDUCTING RESEARCH
WITH PERSONS WHO HAVE SCHIZOPHRENIA

Schizophrenia is a devastating disease affecting approximately 1% of the world’s population over the age of 18 years. In the United States, this is comparable to 7.2 persons per 1,000 total population, and it is estimated that 100,000 are diagnosed with schizophrenia in the United States yearly (National Institute of Mental Health, 2006). Roberts (2006) acknowledges that schizophrenia not only disrupts cognitive abilities of the individual, but the disease process erodes the ill person’s relationships, personal strengths, and societal roles. These factors generate potential vulnerabilities that may be exploited by human researchers. This potential has been an ongoing concern and challenge for research in this population. This article provides (1) an overview of decision making ability and informed consent, (2) measures of decision making ability, (3) research on decision making ability, (4) research interventions to improve informed consent, and (5) an illustration of informed consent process and comprehension in a smoking-related research study.

Overview of Decision Making Ability and Informed Consent

Throughout the 19th century, those with mental illness were believed to lack decision making capabilities, could not make valid decisions, and were thus treated as exceptions
to the norm of any type of consent requirements (Appelbaum & Grisso, 1995). Involuntary hospitalizations of the mentally ill were widespread as families or designated overseers of the indigent had authority to make decisions on involuntary hospitalizations. Despite the implementation of procedures for voluntary hospitalizations in the late 1880’s, the issue of consent to treatment does not appear to have been raised.

The National Commission for the Protection of Human Subjects and Behavioral Research was created in 1974 after the disclosure of the exploitation of subjects in the Tuskegee study of syphilis to discuss special problems of the use of vulnerable populations as research participants (Michels, 1999). Its report entitled *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (also known as the Belmont Report) paved the way for the now known Common Rule issued in 1991 (Michels). The Common Rule provides basic regulations of research on human subjects conducted in federal government or in facilities receiving federal funding (Moreno, Caplan, & Wolpe, 1998). It recognizes special needs of vulnerable populations and required that institutional review boards include additional safeguards to protect their rights. However, the Common Rule does not provide specific guidelines on how to do this (Michels, 1999). The basic components of these doctrines include respect for persons, beneficence, and justice as the primary principles underlying ethical research with human beings. Methods used to recognize these principles included risk /benefit analysis, informed consent, and appropriate selection of subjects.

Informed consent has three requirements to be considered valid. These include (1) the provider is responsible to provide information on the nature and purposes of the proposed procedure, probable benefits, likely risks, alternatives including no treatment, and
voluntary withdrawal, (2) patients must have the opportunity to make decisions without coercion by those providing care, (3) patients must be competent to make the treatment decision. Since a person participates in the decision making process, the rationale of informed consent is undermined with persons with incapacities (Michels, 1999). The Belmont Report specifically notes that comprehension may be limited in potential subjects, such as children, mentally disabled, terminally ill, and the comatose. In these cases, a substitute decision maker was to be called upon to act in that person’s best interest.

The latest federal panel to address the issue of human research subjects was the National Bioethics Advisory Commission (NBAC) which released its report in 1998. The report focused on the heightened vulnerability of mentally ill persons with impaired decision-making capacity. This coincided with a time when the assumptions that the mentally ill were deficient in decision-making abilities began to be questioned (Appelbaum & Grisso, 1995). Some mental health providers felt that those with mental illness may have either no or selective impairment and could thus give informed consent. Appelbaum and Grisso noted that cognitive functioning deficits differ across diagnostic groups and that symptoms of mental illness may fluctuate depending on the severity of the disorder. The capacity to consent is integral to ethical conduct of both clinical care and research.

Appelbaum and his colleagues (Appelbaum & Roth, 1982; Appelbaum & Grisso, 1995) describe four dimensions for determining decision-making capability; these are generally known as (1) understanding, (2) appreciation, (3) reasoning, and (4) expression of a choice. Each standard as delineated by Appelbaum and Grisso is discussed briefly.
The importance of the patient’s comprehension of information is stressed in the first standard as ability to understand relevant information. This information that must be understood reflects that of the three requirements for informed consent. The second standard, ability to appreciate the nature of the situation and its likely consequences, differs in that this requires patients to be able to apply the information to their own situations. For example, patients may understand that their provider believes that they are ill, but they do not believe that they are ill despite the ‘evidence,’ or they may understand that an effective treatment exists, but that the treatment will most likely not help them. Inherent in this standard is that the patient must appreciate the nature and consequences of the decision. The third standard, ability to manipulate information rationally, relates to the ability to use logical processes to compare risks and benefits of options. This standard refers to the logic used in processing information, not the choice that is made. The fourth standard, ability to communicate a choice, is the ability to make a decision. Patients who fail to meet this standard are those who cannot reach a decision or indicate their choice due to their illness/disease as well as those who vacillate to such a degree that treatment cannot be implemented.

This groundwork has been utilized by researchers who study the mentally ill to ascertain the impact or relationship of mental illness to decision-making capabilities. Schizophrenia has a variable course so symptoms and functional impairment fluctuate over time. Approximately one-half of acutely ill hospitalized patients with schizophrenia experience substantially impaired decision-making abilities such as understanding, appreciation, and reasoning (Appelbaum & Grisso, 1995). Since many of these impairments appear to be associated with active symptoms, it is likely that the prevalence
of symptoms is lower among outpatient groups. Fear of the mentally ill by the general population and the accompanying stigma of mental illness have fostered specialized healthcare centers for these persons. These mental health care clinics have been sites to recruit research participants. As a result, clinical psychiatric research is performed largely in the outpatient setting (Michels, 1999). The very nature of informed consent, will most likely exclude those with severe exacerbations.

Measures of Decision Making Ability

Mental health law has been based on a presumption that as a group the mentally ill differ from the non-mentally ill in their decision-making abilities; however, data on the decision-making performance of persons with mental illness are limited. The National Bioethics Advisory Commission Report (1998) focused on the heightened vulnerability of psychiatric patients to impaired decisional capacity. Subsequently, researchers increased their attention to determining patient’s capacity to understand the risks, benefits, and significance of participating in research studies, which culminate in the patient making a rational decision regarding participation. Patients with debilitating mental illnesses may understand and use only a portion of the information provided by consent forms (Kleinman, Schachter, Jeffries, & Goldhamer, 1993; Schachter, Kleiman, Prendergast, Remington, & Schertzer, 1994).

Appelbaum (2006) relates the last decade’s research of presence of schizophrenia and competence to enter research to the availability of conceptually sound instruments to measure abilities related to decision making. The most widely used instrument, the MacArthur Treatment Competence Assessment Tool for Clinical Research (MacCAT-CR), is designed to assess capacity in clinical research settings. This semi-structured
interview yields scores for the four commonly recognized dimensions of decisional capacity of understanding (range 0-26 points), appreciation (range 0-6 points), reasoning (0-8 points), and expression of a choice (0-2 points). While the instrument provides a comprehensive view of the subject’s capacities, a disadvantage is the 15-20 minutes required to administer the instrument (Appelbaum, 2006).

A five-item questionnaire, Evaluation to Sign Consent (ESC), is geared to assess subject’s understanding of key aspects of a study. Although it correlates with the understanding dimension of the MacCAT-CR, it does not measure appreciation, reasoning, or expression of choice (De Renzo, Conley, & Love, 1998).

A briefer three-item questionnaire screening instrument addressing three of the most important aspects of informed consent (the study’s purpose, risks, and benefits) showed strong correlation with the MacCAT-CR understanding scores, and moderate significant correlations with appreciation and reasoning (Palmer et al., 2005). The optimal cutoff score (2.5 points out of a possible 6 points) for the screening instrument provided 100% sensitivity and 77% specificity. This questionnaire was examined with three groups of participants consisting of outpatients with schizophrenia/schizoaffective disorder (n=35), mild to moderate Alzheimer disease (n=30), and diabetes mellitus (n=36). The informed consent related to a hypothetical 12-week study of a randomized controlled trial of an experimental compound being tested for its cognitive enhancing effects. After reviewing the informed consent, they completed the three-item questionnaire followed by the MacCAT-CR individualized for the study. The patients with the highest mean scores were those with diabetes mellitus while those with Alzheimer disease scored the lowest with the schizophrenia group being intermediate. However, considerable heterogeneity
was noted within each group. A consistent correlate of decision-making capacity was cognitive ability which had particularly strong correlations with understanding. The total scores of the three-item questionnaire were significantly correlated with scores of the MacCAT-CR with understanding dimension \( r=0.74; p<.001 \), and to a smaller degree with appreciation dimension \( r=0.41; p<.001 \), and reasoning dimension \( r=0.44; p<.001 \). However, expression of choice dimension was not related \( r=0.12 \) and \( p=.10 \). The researchers concluded that the use of a shorter screening tool with high sensitivity and acceptable specificity would provide researchers an ability to identify persons who would be appropriate for more comprehensive capacity evaluations.

Research on Decision Making Ability

Many psychiatric researchers have challenged the assumption that persons with mental illness are at a higher risk of being exploited due to the effects of mental illnesses on decision-making capacity (Vogel-Scibilia, 1999; Bonnie, 1997). Others propose that there are those with mental illnesses who retain substantial decision-making capacity and to single out this research group not only reinforces the social stigma of mental illness, but could hinder needed psychiatric research (Carpenter, & Conley, 1999; Michels, 1999, Appelbaum, 1999).

The following studies on decision-making abilities found that while patients with schizophrenia as a group had lower scores than those without neuropsychological impairment on decisional making capacity, they had higher performance than patients with dementia. The performance of those with schizophrenia was highly variable with some performing at a level similar to the control participants. Poorer performance correlated most strongly with neuropsychological impairment. Cognitive ability was
strongly associated with decisional capacity, while negative and disorganized symptoms were strongly associated with decreased decisional capacity. Interestingly, psychotic symptoms such as delusions and hallucinations did not have this association.

*Decision-Making Abilities*

In a pilot study (Grisso & Appelbaum, 1991), impairments in decision-making abilities were studied across three inpatient groups with either schizophrenia or schizoaffective disorder, major depression or bipolar disorder, or ischemic heart disease, and one outpatient group with no major mental health or medical disorder. The instrument, Measuring Understanding of Disclosure, assessed individual understanding of typical information required for disclosure in informed consents for treatments involving medications. Each participant received one medical and one mental health standardized disclosure of informed consent form. Instruments were administered in three protocols: (a) uninterrupted with entire disclosure completed before asking standardized questions; (b) single-unit disclosure with a unit of informed consent presented and standardized questions immediately following each unit; (c) single-unit recognition with a unit of informed consent presented and participants then asked to identify after each unit if the four presented statements were similar to or different from the given information. There was a significant difference across the four groups on all three methods of administration. Generally, performance was better for all groups on the single-unit disclosure and recognition methods than on the uninterrupted disclosure. The schizophrenic group had significantly poorer understanding of informed consent disclosures about potential medication on both mental and medical illness forms on each of the protocols than did the other groups. The researchers noted that the results did not support the generalized
presumptions about decision-making abilities of those with schizophrenia. The
schizophrenic participants had a considerable range of scores with some performing at a
level similar to the means of the non-mentally ill participants. Findings suggested that
poorer understanding may be greater in those with more severe schizophrenic symptoms
based on results of the Brief Psychiatric Rating Scale (BPRS) and those experiencing first
mental health hospitalization in late adolescence or early adulthood.

Following this pilot study, a full-scale multi-site study (Grisso & Appelbaum, 1995)
was conducted with 498 similar participants. The study’s findings were similar to those
of the pilot. Hospitalized patients with mental illness, particularly those with
schizophrenia, displayed deficits in decision-making capacity more often than the
medically ill and control groups. However, approximately half of those with
schizophrenia performed well on all measures combined while a majority performed
adequately on any particular measure. Participants with more severe psychiatric
symptoms, such as delusions and disorganized thinking, performed poorly.
Approximately three fourths of those with major depression performed well on all
measures and demonstrated intermediate levels of decision-making capacity. The
hospitalized medically ill patients performed almost on a level with those of the control
group. The researchers concluded that mental illness does not necessarily impair one’s
decision-making capacity.

*Competence to Consent*

Attention has been drawn to the issue of the competence of persons with severe
mental illness to consent to participate in clinical research by recent high-profile cases
that have cast shadows over research among mentally ill persons, including those with
schizophrenia (Hilts, 1994). The MacCAT-CR, a structured instrument designed to aid in assessment of competence to consent to clinical research, was administered to two groups to compare their competence-related abilities (Kovnick, Appelbaum, Hoge, & Leadbetter, 2003). These groups were comprised of long-term hospitalized persons with schizophrenia (n=27) at a state hospital and a comparison group (n=24) without schizophrenia or any past psychiatric hospitalizations. Inpatients with schizophrenia performed more poorly on competence measures with significantly lower scores on measures of understanding, reasoning, and appreciation than the comparison group. However, when inpatient results were compared to a cutoff for adequacy of performance, defined as a score equal to or better than the worst-performing comparison participant, 33% performed as well as the comparison participant on each of the subscales. In addition, 89% obtained a score equal to or above the lowest-scoring comparison participant on at least one of the subscales. The researchers concluded that neither diagnosis nor length of hospitalization implied a person’s lack of capacity to make decisions or give informed consent to participate in research.

The degree to which persons with impaired cognitive functioning and psychiatric symptoms could give informed consent was examined in persons with schizophrenia and those with HIV (Moser, et al., 2002). The HIV group was seen to have commonalities with schizophrenia persons in that they have an ongoing illness that can negatively impact psychiatric and cognitive status and both groups are frequently asked to participate in research studies. All subjects were between the ages of 18-55 with 25 in each group and more inpatients in the schizophrenia group. The subjects were asked to participate in a hypothetical drug study consisting of a 6-week, randomized, double-blind,
placebo-controlled study of a cognition-enhancing medication. Decisional making capacity was assessed with the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) and a shorter questionnaire, Evaluation to Sign Consent, which assesses the participant’s understanding of disclosed information. Compared to the HIV group, the schizophrenia group had lower mean scores on the MacCAT-CR on all categories of decision-making capacity, but was statistically significant only for understanding and appreciation. On the Evaluation to Sign Consent, 20 of the schizophrenia group and 24 of the HIV group were assessed to have adequate understanding to provide consent to the hypothetical study. Participants also had lower scores on the understanding measure of the MacCAT-CR. Cognitive ability was strongly associated with decisional capacity in the schizophrenia group. In addition, negative and disorganized symptoms were significantly associated with decreased decision-making capacity in the schizophrenia group; however, psychotic symptoms did not have this association. The researchers noted lacking a remedial intervention as a limitation of the study; they suggested that categories of the MacCAT-CR which score less than half of the possible points raise concern for a need for remediation.

Carpenter and his colleagues (2000) found that long-stay schizophrenic inpatients who did not respond to treatment performed significantly more poorly than a healthy comparison group on decision-making capacity. To explore this further, Kovnick, Appelbaum, Hoge, and Leadbetter (2003) conducted a study of 27 long-stay psychiatric inpatients with diagnosis of schizophrenia or schizoaffective disorder and 24 persons from the community as a control group. The study described a hypothetical clinical trial of a new medication for treating schizophrenia; the control group was instructed to
assume that they suffered from schizophrenia and to answer the questions from their own perspective. The MacCAT-CR was used to assess decision-making capacity. Inpatients performed more poorly on the competence measures than did the control group; significantly lower scores occurred on measures of understanding, reasoning, and appreciation. The Brief Psychiatric Rating Scale (BPRS) scores, measuring symptom constructs of schizophrenia, were correlated with performance on the MacCAT-CR with greater psychopathology being correlated with higher impairments on decision-making capacity. Significant negative correlations were seen with total score of the BPRS and its withdrawal subscale for understanding and appreciation measures. While the total scale and reasoning did not have a similar significant negative correlation, it was in the same direction. There was a significant negative correlation between the length of hospitalization and measures of understanding, reasoning, and appreciation. Verbal cognitive functioning was both significantly correlated with measures of understanding and appreciation in both groups. They noted that 33% of the inpatients scored as well as the lowest performing control participant on each of the measures and that 89% scored above or equal to the lowest control participant on at least one measure. They concluded that neither the diagnosis of schizophrenia nor long-stay hospitalization precludes a person from having the capacity to make decisions and give informed consent to participate in research.

The ability to obtain informed consent in middle-aged and older persons (40 years of age or older) with schizophrenia may be more challenging as cognitive changes associated with aging may have an adverse impact on decision-making capacity (Palmer, Dunn, Appelbaum, & Jeste, 2004). These researchers studied the range, stability, and
correlates of decision-making capacity related to treatment of a hypothetical study of
treatment with an atypical antipsychotic medication. The control group was instructed to
imagine they had the condition described in the disclosure form. Participants included 59
middle-aged and older outpatients (mean age of 50.2, SD= 6.8) with schizophrenia or
schizophrenia affective disorder and 38 control participants (mean age of 56.8, SD=9.2).
The control group had significant positive correlations between cognitive abilities
measured by total score of the Mattis Dementia Rating Scale (MDRS) and the MacCAT-
CR reasoning measure and between the memory subscale score of the MDRS and the
MacCAT-CR understanding measure. The MDRS memory subscale accounted for
significant additional variance in the measure of understanding. The MDRS
conceptualization subscale score accounted for significant additional variance in the
measure of reasoning. The cognitive ability score of Abstraction/Cognitive Flexibility
accounted for significant additional variance in the measure of expression of a choice. At
a one-month follow-up, the test-retest correlations were highly significant for
understanding, appreciation, reasoning, and expression of a choice. The researchers
concluded that level of decisional making capacity was not associated with age or
severity of psychology, but was strongly associated with cognitive test performance. The
patients’ decisional capacity remained stable during the one-month follow-up.

The question of whether persons with acute mental illnesses were more likely than
other persons to consent to higher risk protocols was studied by Cohen and colleagues
(2004). The study had two groups consisting of inpatients who had been admitted with
either a diagnosis of major depression (n=21) or schizophrenia (n=22) and a third group
consisting of persons (n=21) living in the community who served as the control group.
All potential participants were informed that the study involved hearing about two
different human research protocols and they would be asked to respond to questions
testing their understanding of the provided information. Out of the potential participants,
29% (6 of 21) of the persons with schizophrenia, 91% (20 of 22) of the major depression
patients, and 95% (20 of 21) of the controls agreed to participate. The participants were
informed that the study was only seeking their opinion if they would be willing to
participate in the studies; no actual consent to participate was being sought. The lower
risk protocol involved a drug study of a six-week, placebo controlled, pharmaceutical
trial of either a new antidepressant (major depression and control group) or a new
antipsychotic drug (schizophrenia group). The drugs had been trialed in animals and
healthy subjects; they were now seeking to study the drugs in a clinical population. The
higher risk study, lasting about three hours, involved the participant receiving a proposed
positron emission tomographic (PET) scan while performing assorted cognitive tasks at
the same time. An individualized MacCAT-CR was administered for each study as the
protocol was explained. More participants in the schizophrenia group had been in
previous research than had the depression group, at 66.7% and 20%, respectively. They
found that mentally ill inpatients being treated for depression or schizophrenia were not
more likely to volunteer in research than the control group. Rather, persons with
schizophrenia and depression were less apt to volunteer for research than the control
group. All control participants chose to participate in either one or both studies contrasted
to 50% of the depressed group and 17% of the schizophrenia group. From these
participants, 50% of the depressed group chose only the drug study and 55% of the
controls chose only the drug study. Only one participant with schizophrenia chose to participate and, interestingly, chose both studies.

The community control group scored the highest on the standardized measures of decision-making capacity followed by the depression group and then the schizophrenia group. The capacity to consent to research scores was not lower for those who agreed to participate in research. In the trial drug study, the depression group scored significantly lower in reasoning than the controls. The schizophrenia group scored significantly lower on understanding, reasoning, and appreciation than both depression and control groups. In the ketamine study, the schizophrenia group scored significantly lower on understanding, reasoning, and appreciation than the depression and control groups. There was no significant difference in study preference by group. The researchers concluded that the mentally ill persons were no more likely to volunteer to participate in a high-risk study with no medical benefit than were the community control participants. The limitations of the study were its small sample size, the selection process of participants as researchers needed to consult with the treating clinician before approaching the patient, and no additional intervention was performed to see if results could be increased.

Candilis and his colleagues (2006) sought to identify variables related to the willingness of subjects with thought disorders to participate in research that could be markers of participant vulnerability. The study involving 52 participants with schizophrenia or schizoaffective disorders, aged 19-59 years, asked them to consider participation in a hypothetical trial of a random blinded exposure to a new antibiotic versus established treatment for a sore throat. When asked if they would choose to participate in the trial, 33 (63.5%) participants said “yes,” while 19 (36.5%) said “no.”
The groups did not differ by gender, age, or race. Participants with more education were more likely to indicate a willingness to take part in the trial. Willingness to participate in the trial was not significantly associated with the Short Form-36 health related quality-of-life instrument, number of years with the disease, perceived disease progression, or anticipated prognosis. Willing and unwilling participants differed significantly on two of the reasons offered for their decision. The willing participants were more likely to mention altruistic considerations while the unwilling participants were more likely to mention an aversion to research. Those who were willing to participate in the trial (1) scored higher in the understanding and expressing a choice dimensions of the MacCAT-CR, (2) scored significantly higher on the Mini-Mental State Examination, (3) scored significantly lower on the total Positive and Negative Syndrome Scale (PANSS) indicating less psychosis, and (4) scored significantly lower on the general scale of the PANSS. The researchers concluded that if better understanding leads to greater willingness to participate, there was support for the informed consent process and the movement toward enhanced informed consent interventions. They noted that when potential participants had vacillating or uncertainty in making a choice, this may raise the researchers’ sensitivity to those with thought disorders.

Summary

In summary, persons diagnosed with schizophrenia are not precluded from being able to give informed consent. There is great variability in the decision-making capacity of this population. As a whole, they perform lower than normal subjects, but some perform on the same level. In addition, they perform better than those with dementia. Negative and disorganized symptoms of schizophrenia have been associated with decreased
decision-making capacity. Limited research in this population does not support a belief that they have decreased decision-making capacities.

Research on Interventions to Improve Informed Consent

The National Bioethics Advisory Commission Report (1998) focused on the heightened vulnerability of psychiatric patients to impaired decisional capacity. Consequently, researchers increased their attention to determining patient’s capacity to understand the risks, benefits, and significance of participating in research studies which culminate in the patient making a rational decision regarding participation. Patients with debilitating mental illnesses understand and use only a portion of the information provided by consent forms (Kleinman, Schachter, Jeffries, & Goldhamer, 1993; Schachter, Kleinman, Prendergast, Remington, & Schertzer, 1994). Recent findings suggest that cognitive impairment is an important determinant of overall decisional making capacity in persons with schizophrenia (Carpenter, et al., 2000; Kovnick, et al., 2003; Moser, et al., 2002; Palmer, et al., 2004; Palmer, et al., 2005). While no single level or pattern of deficits in cognitive functioning is present in persons with schizophrenia, the most commonly occurring deficits are in learning new information, attention/working memory, and executive functions (Hendricks & Zakzanis, 1998). Researchers thus began exploring various interventions to enhance the decision-making capacity of persons with schizophrenia. Table 1.1 provides a summarization of these five studies.

In summary, this paucity of available studies had a predominantly male population with a high school educational level. Patients’ recall or understanding improved with a variety of interventions, including shorter, better organized, or simplified and illustrated
informed consent formats. Improvement was shown when participants received
electronic-assisted informed consents, received corrected feedback, had multiple trials,
received an alert to information to be presented, or were provided summaries of
information. Challenges in this population’s abilities to recall or understand informed
consent may be overcome with informed consent design and educational interventions.

Results of a Pilot Study with Use of Bupropion in Schizophrenics who Smoke

The diagnosis of schizophrenia does not in itself limit one’s decision-making capacity
or ability to provide informed consent. Most of the studies have included outpatients with
schizophrenia; these patients may not be as compromised as those in inpatient or
supervised living situations. A research study was conducted in a rural Veterans Affairs
Medical Center in Ohio to obtain information on smoking in people with schizophrenia
who resided in supervised residential care homes and to evaluate how smoking may be
affected by the combination of bupropion sustained release with antipsychotic
medications. The study examined whether bupropion decreased the amount of smoking in
patients with schizophrenia over an 8-week period and whether results differed with
different types of antipsychotic medications.

In relation to informed consent, each subject was provided a hard copy of the
informed consent and an electronic version which highlighted key points of the study. A
research assistant read aloud from the electronic version which was visible to the subject.
The subject was asked to follow along with the informed consent while being read aloud.
To assess the comprehension of the subject’s understanding of the study, a nine-item
comprehension questionnaire was administered to the subject after the reading of the
informed consent. Any item that was missed was re-explained to the subject and the
complete questionnaire was re-administered. The study’s protocol was described at the beginning of the study and included the following: visits at the beginning of the study, after two, four, and eight weeks; bupropion sustained release tablets would be added to their usual medication regime during the study; and that various measures would be taken during the study including weight, vital signs, how a cigarette was smoked (topography), measure of carbon monoxide, a blood specimen for measures of nicotine and nicotine metabolite cotinine, assessment of schizophrenia symptoms, involuntary movements, and mood.

Potential participants were informed that while there may not be a direct medical benefit to them, the researchers hoped the information learned from the study would benefit other patients with schizophrenia who smoke. Potential benefits were stated as more frequent medical exams and a possible reduction in the amount of cigarette usage. They were informed that (a) there were other available choices to help stop smoking, (b) bupropion could be prescribed without study participation, (c) participation was voluntary, (d) every effort would be made to maintain the confidentiality of study records, (e) there was no charge for the study’s tests or medications, (f) participants were responsible to pay for their own cigarettes, and (g) they would be compensated at each visit. They were also informed that investigators would tell them about new information that may affect their health, welfare, or willingness to stay in the study. They were asked if they had any questions about the study. Informed consent was not completed until they had received satisfactory answers to any questions.

The 9-item consent form comprehension questionnaire was completed correctly on Trial 1 by 38 of the 49 participants (78%). Of the 11 who did not respond correctly to all
nine items on the questionnaire on Trial 1, one subject scored five; two scored seven, and eight scored eight. Questions on number of visits in the study and potential risks or discomforts were missed most frequently with 7 and 5 errors, respectively. After the research assistant reviewed with the involved participant the information related to the specific missed question(s), each answered correctly on Trial 2. (Table 1.3)

The scores of those responding correctly to all nine items of the consent form comprehension questionnaire were correlated to scores of the Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30-item, seven point rating instrument based on a formal semi-structured interview and other informational sources such as family or staff to evaluate the positive and negative dimensions of schizophrenia. Seven items are in each category of negative and positive symptoms with 16 items in general psychopathology. The positive symptoms of schizophrenia include delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. The negative symptoms of schizophrenia include a blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversion, and stereotyped thinking. The general psychopathology relates to the interviewer’s observations, e.g., tension, mannerism, disorientation, poor attention, anxiety, guilt feelings, and poor impulse control (Sajatovic & Ramirez, 2001).

Using Pearson correlations with significance level at $p=0.05$, significant correlations were present with PANSS and the number of correct responses at Trial 1 of the 9-item comprehension questionnaire (Table 1.4). The total informed consent comprehension score correlated negatively with the positive subscale of the PANSS and with the sum of
negative subscale. These results are consistent with other studies (Appelbaum & Grisso, 1995; Candilis, et al., 2006) which found that increased negative symptoms and more severe schizophrenia symptomology were associated with decreased decisional capacity and poorer understanding of informed consent. These results serve to alert a researcher that these subjects may have more difficulty in understanding a study and its protocol and that further strategies to improve their understanding may be indicated.

Conclusion

Informed consent is generally a prerequisite for clinical research. Protecting the rights of research participants is a concern particularly with those who suffer from disorders that may impair their cognitive functioning and capacity to provide informed consent. However, the degree to which persons with schizophrenia lack the capacity to make their own decisions about research participation remains unclear. While as a group they perform worse than subjects without neuropsychological impairment, there is wide variability in this population. In addition, various educational interventions have demonstrated effectiveness in bringing them up to an acceptable level of performance in understanding aspects of informed consent. The diagnosis of schizophrenia does not necessarily imply that a person lacks the capacity to make decisions and give informed consent to participate in research. The research in this arena is young and begs the need for the development of a reliable means of measuring consent-related capacities.
<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Age</th>
<th>Gender</th>
<th>Education</th>
<th>Intervention Type</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wirshing et al. (1998)</td>
<td>SCHZ n=49</td>
<td>46.5 (SD=8.5)</td>
<td>94% male</td>
<td>13.0 (SD=1.8)</td>
<td>When a subject did not respond correctly to item on a questionnaire of critical items of informed consent, that portion was re-explained and questionnaire readministered. Procedure completed until all items were answered correctly. Questionnaire was repeated 7 days later. If item was missed, item was explained until subject stated understanding and answered correctly on questionnaire.</td>
<td>Median score on first trial was 80% 53% required 2 trials to obtain 100% 37% required 3 or more trials to obtain 100% Group scores improved between first trial and Day 7. Conceptual disorganization on BPRS was correlated to percentage of correct responses on Day 7. Remediation resulted in increased comprehension and retention of information.</td>
</tr>
<tr>
<td>Stiles et al. (2001)</td>
<td>SCHZ n=77</td>
<td>Not described</td>
<td>SCHZ Group 69% male</td>
<td>SCHZ Group 12% college degree 18% less than high school</td>
<td>2 manipulated factors (1) Use of a typical or a graphically enhanced disclosure form (2) Presence or absence of third-party facilitator who stopped reading at end of each section to have subject state main points, allow subject to ask questions, and urge subject to seek clarification at end of section. For the group with a facilitator, recognition test was administered one time. (3) For the non-facilitator group, any subject who failed to attain 100% on recognition test received feedback on missed items and was retested. Two feedback and retest sessions were allowed.</td>
<td>Mean recall and recognition scores of SCHZ group was significantly lower than depressed and control groups. Neither the type of disclosure form nor presence of facilitator was associated with higher scores. The use of feedback was associated with increased understanding in all groups. Scores were higher in each group when measured by recognition (multiple choice) rather than recall (paraphrase). Significant interaction between consent process and diagnostic groups was noted; control and depressed groups had higher recognition scores with the facilitator process whereas SCHZ group had higher score with standard disclosure process.</td>
</tr>
</tbody>
</table>

Table 1.1
Studies Examining Methods to Improve Consent in Schizophrenic Persons
Table 1.1 continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Gender</th>
<th>Education</th>
<th>Intervention Type</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunn et al. (2002)</td>
<td>SCHZ n=80</td>
<td>SCHZ Group Routine Consent (n=41)</td>
<td>61% male</td>
<td>Routine Consent</td>
<td>SCHZ Groups Routine Consent 12.4 (SD=1.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhanced Consent (n=39)</td>
<td></td>
<td>Enhanced Consent 12.4 (SD=2.8)</td>
<td>Routine consent had staff member read aloud consent form; subject had a copy to follow along; at predetermined points, stops were done to answer any questions of subject. Enhanced consent consisted of computerized slide show incorporating more structure and review of important information. Only this format differed from routine consent.</td>
</tr>
<tr>
<td></td>
<td>n=19</td>
<td>SCHZ n=19 Control Group Routine Consent (n=10)</td>
<td></td>
<td>Control Group</td>
<td>Control Group Routine Consent 13.7 (SD=1.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhanced Consent (n=9)</td>
<td></td>
<td>Routine Consent 14.2 (SD=2.0)</td>
<td>Control group obtained higher comprehension scores than SCHZ group. Both groups had higher scores on Trial 1 with enhanced consent. Greater proportion of enhanced consent. SCHZ group scored 100% on Trials 1 and 2 than did routine consent SCHZ groups. Post-test scores did not differ significantly between enhanced consent SCHZ group and routine consent control group. In SCHZ group, level of education and cognitive performance with comprehension test scores.</td>
</tr>
</tbody>
</table>

Eyler et al. (2005) | Total n=44 | Standard administration n=20 | 50% male | Standard administration condition had examiner read aloud from the paper consent form. In experimental conditions, examiner asked questions on a flipchart at predetermined times to probe subjects’ understanding the difference was that in corrective feedback, the answer was given after the question and subject’s response. In errorless learning, the subject received the correct answers just prior to the question. |
|                  | SCHZ n=12 | Corrective feedback condition n=20 | 50% male | Corrective feedback condition 11.7 (SD=1.3) | Errorless learning subjects made fewer understanding errors in concurrent learning than corrective feedback subjects. Post-consent understanding was higher in both experimental groups compared to standard approach. Concurrent understanding scores on both experimental groups were significantly higher than post-consent understanding scores. In both experimental groups, concurrent understanding of all items was significantly correlated with post-consent understanding of all items. |
|                  | standard administration n=20 | Corrective feedback condition 11.7 (SD=2.4) |          | Corrective feedback condition 11.7 (SD=1.3) | Errorless learning subjects made fewer understanding errors in concurrent learning than corrective feedback subjects. Post-consent understanding was higher in both experimental groups compared to standard approach. Concurrent understanding scores on both experimental groups were significantly higher than post-consent understanding scores. In both experimental groups, concurrent understanding of all items was significantly correlated with post-consent understanding of all items. |
|                  | corrective feedback condition n=12 | Errorless learning condition 45.2 (SD-11.5) |          | Errorless learning condition 12.0 (SD=1.8) | Errorless learning subjects made fewer understanding errors in concurrent learning than corrective feedback subjects. Post-consent understanding was higher in both experimental groups compared to standard approach. Concurrent understanding scores on both experimental groups were significantly higher than post-consent understanding scores. In both experimental groups, concurrent understanding of all items was significantly correlated with post-consent understanding of all items. |
|                  | errorless learning condition n=12 | Errorless learning condition 50% male |          | Errorless learning condition 50% male | Errorless learning subjects made fewer understanding errors in concurrent learning than corrective feedback subjects. Post-consent understanding was higher in both experimental groups compared to standard approach. Concurrent understanding scores on both experimental groups were significantly higher than post-consent understanding scores. In both experimental groups, concurrent understanding of all items was significantly correlated with post-consent understanding of all items. |
Table 1.1 continued

<table>
<thead>
<tr>
<th>Author</th>
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<th>Gender</th>
<th>Education</th>
<th>Intervention Type</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wirshing, et al.</td>
<td>N=25 SCHZ N=25 control (college students)</td>
<td>SCHZ 37.9 (SD=7.4)</td>
<td>SCHZ 18 male 2 female</td>
<td>SCHZ 12.0 (SD=1.8)</td>
<td>The consent is read aloud; then, subjects were administered the uncued recall test of 8 items in informed consent. No feedback was given on correctedness of response. After a 5-minute distracter task, the same questions were presented in a cued recognition (multiple choice) format.</td>
<td>Both groups had significantly higher recognition scores than recall screen. Recall scores significantly higher in control group. SCHZ group not significantly lower overall understanding scores. Lower recall scores and higher thought disorder ratings were related. Lower recognition scores and higher disorganization ratings were related. With use of cues in the recognition test, scores of the SCHZ group approached those of the control.</td>
</tr>
<tr>
<td>Moser et al.</td>
<td>N=30 SCHZ N=30 control</td>
<td>SCHZ 34.10 (SD=10.65)</td>
<td>SCHZ 22 men 8 women</td>
<td>SCHZ 12.72 (SD=2.81)</td>
<td>After decisional capacity was assessed with Mac CAT-CR. SCHZ group received computerized presentation of study’s information with one key point per slide. Subjects read along as examiner read aloud. Mac CAT-CR understanding items which did not receive full credit were reviewed with subject. Corrective feedback provided to subject on any confusing part of the protocol. Mac CAT-CR was repeated.</td>
<td>At baseline, SCHZ group had significantly lower scores on understanding. After the intervention, SCHZ group had statically significant improvement in understanding and was not significantly different from control group on any Mac CAT-CR domains.</td>
</tr>
<tr>
<td>Age</td>
<td>Gender</td>
<td>Race</td>
<td>Educational level</td>
<td></td>
<td></td>
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<tr>
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</tr>
<tr>
<td>Range=46-67</td>
<td>Male=48 (98%)</td>
<td>White=36 (73%)</td>
<td>Grade 8=2 (4.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean=50.5</td>
<td>Female=1 (2%)</td>
<td>Black=13 (27%)</td>
<td>Grades 9-11=7 (14.2%)</td>
<td></td>
<td></td>
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<tr>
<td>SD=5.5</td>
<td></td>
<td></td>
<td>Grade 12=26 (53.1%)</td>
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<td></td>
<td></td>
<td></td>
<td>GED=4 (8.2%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Grades 13-14=10 (20.4%)</td>
<td></td>
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</tbody>
</table>

Table 1.2
Demographics of 49 study participants
1. The purpose of this research study is to obtain information on smoking in people with schizophrenia and to evaluate how smoking may be affected by the combination of bupropion sustained release with antipsychotic medications.

   True  False

2. The length of the study is _______ weeks.

   1  5  8  10

   8

3. I will have ________ visits to the Veterans Affairs Medical Center for the study.

   2  4  6  8

   7

4. The records of this research study are not confidential and may be given to anyone.

   True  False

5. There are no risks or discomforts associated with my participation in this research study.

   True  False

6. The most common side effects seen with bupropion included agitation, insomnia, dry mouth, nausea, vomiting, tremors, headache, and constipation.

   True  False

7. As part of the study procedures, I will smoke my regular brand of cigarettes through a small device to measure how I smoke.

   True  False

8. As part of the study procedure, I will have my blood drawn.

   True  False

9. My participation in the study is entirely voluntary and I can withdraw at any time.

   True  False

Table 1.3
Number of incorrect responses on consent form comprehension questionnaire of 49 participants
### Table 1.4

Pearson correlations with PANSS and scores on informed consent comprehension questionnaire at trial 1

<table>
<thead>
<tr>
<th>Subscale of PANSS Instrument</th>
<th>Total Score Informed Consent Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive Subscale</strong></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.332</td>
</tr>
<tr>
<td>p Value</td>
<td>.020*</td>
</tr>
<tr>
<td><strong>Negative Subscale</strong></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.291</td>
</tr>
<tr>
<td>p Value</td>
<td>.043*</td>
</tr>
<tr>
<td><strong>General Subscale</strong></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.131</td>
</tr>
<tr>
<td>p Value</td>
<td>.388</td>
</tr>
</tbody>
</table>

* p<.05 (two-tailed).


CHAPTER 2

PHARMACOTHERAPY INTERVENTIONS IN SMOKERS WITH SCHIZOPHRENIA

Smoking is the single greatest preventable cause of illness and premature death in the United States. People who smoke are at increased risk of cancer, lung disease, heart disease, and other smoking related illnesses that contribute to over 440,000 deaths a year. The estimate of medical care costs attributable to smoking or smoking related illnesses, coupled with the value of lost productivity, exceeds $167 billion annually (United States Public Health Department [USPHD], 2005). Tobacco dependence is a chronic condition that often requires repeated intervention to quit. Of those smokers who try to quit, those who have the support of their physician or healthcare provider are the most successful (USPHD, 2005).

Persons with mental illness smoke at higher prevalence than those without mental illness, have lower cessation rates, and reflect a large population of the tobacco markets in the United States (Lasser, et al., 2000). An estimated 26.2% of adult Americans, or one in four adults, suffer from a diagnosable mental disorder in a given year (Kessler, Chiu, Demler, & Walters, 2005). However, a much smaller proportion of adult Americans of 1 in 17 (6%) suffer from a serious mental illness (National Institute of Mental Health [NIMH], 2006). Persons with active mental illness are almost twice as likely to smoke. Lasser and his associates reported current smoking prevalence for
respondents with no mental illness as 22.5%, respondents with mental illness at any time in their lives as 34.8%, and respondents with active mental illness in the past month as 41.0%. Psychiatric patients are two-to-three times more likely to develop and maintain a nicotine addiction (Ziedonis, Kosten, Glazer, & Frances, 1994).

Approximately 1% of American adults have schizophrenia (NIMH, 2006). The Veterans Healthcare System which operates the largest mental health system in the United States has a prevalence of schizophrenia in these veterans at 4.6% (Health Services Research and Development, 2001). Nicotine dependence is the most common substance use disorder among persons with schizophrenia. Among samples of patients with schizophrenia, 74-83% smoke cigarettes (George, et al., 2000). Furthermore, persons with schizophrenia are more likely to be heavy smokers, defined as smoking more than 1 ½ packs a day (Lohr & Flynn, 1992). Factors that contribute to increased use and consumption include potential positive effect of nicotine on neurotransmitter systems involved in schizophrenia, increased nicotine withdrawal symptoms in persons with schizophrenia, nicotine mitigation of side effects of psychotropic medications, and social factors such as lower income and educational levels (Jarvis & Wardle, 2005). Nicotine is thought to interact with many of the same pathways believed to be aberrant in schizophrenia. Nicotine seems to have an important role in modulating both dopamine and glutamate transmission and may impact on the negative and positive symptoms of schizophrenia. Persons with schizophrenia use nicotine to self-medicate negative symptoms of amotivation, dysfunctional relationships, and affective blunting (Ziedonis, et al., 1994). Patkar and colleagues (2002) found significant positive correlations between nicotine dependency measured by Fagerstrom Test for Nicotine Dependence and
total negative symptom scores and its subscales of blunted affect, social withdrawal, difficulty in abstract thinking, and stereotyped thinking, and in general psychopathology subscales of unusual thought content, disorientation, poor attention, and poor impulse control.

Schizophrenia is associated with difficulty in processing sensory information. Individuals with schizophrenia have an impaired ability to filter out background noise in the environment thus interfering with attention and processing sensory stimuli. Nicotine has the ability to temporarily normalize auditory gating and thus decrease difficulty with processing sensory information (Adler, Lee, Hoffer, Wiser, & Freedman, 1993). Nicotine has also demonstrated the ability to improve visuospatial working memory function in schizophrenia (George, et al., 2001). Persons with schizophrenia also smoke to alleviate some of the uncomfortable side effects of psychotropic medications (Miller, Kelly, & Perry, 1990). Smoking increases the metabolism of psychotropic medications and patients with schizophrenia who smoke receive higher doses of neuroleptics than non-smokers (Ziedonis, Koster, Glazer, & Frances, 1994). The purpose of this paper is to (1) summarize biological measures of nicotine dependence, (2) review pharmacotherapies utilized in smoking cessation, and (3) explore studies using these pharmacotherapies and biological measures in smokers with schizophrenia.

Theoretical Definitions of Nicotine Dependence

Nicotine dependence meets the DSM-IV-TR criteria for substance-related disorders (American Psychiatric Association, 2006). These criteria require the presence of at least three of the following criteria occurring at any time in the same 12-month timeframe. These include (1) tolerance as defined by either needing increased amounts of the
substance to obtain desired effect or marked decreased effect with continued use of the same substance amount, (2) withdrawal as evidenced by a need for continued use to avoid withdrawal symptoms or use of a closely related substance to relieve or avoid withdrawal symptoms, (3) substance is often taken in larger amounts or over a longer period than intended, (4) unsuccessful efforts or persistent desire to cut down or control use, (5) considerable time is spent in activities necessary to obtain, take, or recover from its use, (6) giving up or reducing attendance at important activities due to use, and (7) continued use despite knowledge that use causes or exacerbates a persistent or recurrent social, psychological, or physical problem.

The Report of the Surgeon General (United States Department of Health and Human Services [USDHHS], 1988) developed a set of criteria to determine nicotine dependence. These criteria included primary and additional indices. The primary criteria were that (1) nicotine dependence is driven by highly controlled or compulsive use or urges which persist despite desire to quit or repeated efforts to quit, (2) nicotine has a mood altering or psychoactive action in the brain as nicotine enters the bloodstream, and (3) the psychoactive chemical is able to function as a reinforcer to directly strengthen behavior and thus lead to more ingestion. The additional criteria helpful in defining this dependence are repetitive and stereotypic behavior; usage despite physical, social, or psychological consequences; relapse; cravings; tolerance; withdrawal; and euphoriant effects.

Nicotine dependence is difficult to conquer. This is due to the complex interplay of nicotine’s pharmacology, behavioral cues, psychological adaptive mechanisms, and other factors such as concern for weight gain that impact the smoker (Wall & McClellan,
2006). In brief, nicotine stimulates several neurotransmitters in the nucleus accumbens resulting in reward consequences of pleasure and arousal; nicotine is known to be associated with a “rush” upon first inhalations of the cigarette, and nicotine is delivered rapidly, within seconds, to the central nervous system (Balfour, 2002). To avoid withdrawal symptoms which can occur within hours of the last smoked cigarette, smokers may model their smoking bouts to avoid or alleviate withdrawal symptoms. Smokers have incorporated smoking into their daily activities making it more difficult to quit; the behavioral cues associated with activities such as smoking after meals or upon arising are strong and lead to smoking reinforcement.

Both the DSM-IV-TR (APA, 2006) and the USDHHS (1998) criteria for nicotine dependence include intake of nicotine. Tobacco use and severity of dependence are related. Biological measures of smoke constituent exposure can be valid indices of nicotine dependence thus providing an objective measure of smoking reduction or abstinence to validate self-reported data of cigarettes smoked (Benowitz, et al., 2002). A potential for overlap of values of biological measures always exists between nonsmokers with an extensive exposure to secondhand smoke or between nonsmokers and occasional or currently absent smokers (USDHHS, 1986). The selection of an appropriate biological measure and utilization of its associated cut-off points for smoking help assess exposure from non-exposure. A discussion of biological measures of nicotine dependence follows.

Biological Measures of Nicotine Dependence

Biological measures include carbon monoxide (CO), nicotine, and cotinine, a metabolite of nicotine. Carbon monoxide can be utilized to validate smoking status for those using all forms of nicotine replacement therapies (NRT) as well as with bupropion
sustained-release therapy (BUP-SR). Cotinine is advantageous for verifying smoking status of those on BUP-SR. Since NRT provides a source of nicotine for the body, cotinine has limited value in identifying smoking status, but it can be useful to confirm use of NRT.

**Carbon Monoxide**

Carbon monoxide, a product of incomplete combustion, is a major constituent of cigarette smoke. With a high affinity for hemoglobin, CO forms carboxyhemoglobin (CO Hb) thus impairing oxygen transport and cellular utilization of oxygen. Expired CO and blood CO Hb are highly correlated (r=.98) (Benowitz & Henningfield, 1994; Jaffe, Kanzler, Friedman, Sturkard, & Vereby, 1981). Although the Federal Trade Commission has established measures of cigarette nicotine and CO levels, these levels have little relationships to the amount actually absorbed (Muranaka, Higashi, Itani, & Shimizu, 1988) since both puff volume and puff intensity influence CO uptake (Eissenberg, Kennedy, Riggins, & Likness, 1998).

Measuring expired CO is simple and relatively inexpensive (once the instrument has been purchased) with results immediately available. Sensitivity and specificity of CO in expired air are 90% and 83% respectively with a cutoff of 6.5 ppm (Deveci, Deveci, Acik, & Ozan, 2004). Exposure to environmental sources of CO such as exhaust and other pollutants may result in CO levels of 2-6ppm (Sonnenworth & Jarrett, 1980). The typical cut-point for assessing smoking abstinence is 8-10ppm (Benowitz, et al., 2002; Cummings & Richard, 1988). The half-life of CO varies with ventilatory patterns. In sedentary activities, the half-life is 2-3 hours; during sleep, the half-life is 4-8 hours, while in exercise it may be as little as 1 hour. During sleep, CO levels decline more
slowly. As a result, some smokers who have not smoked overnight may have levels as high as 30 ppm upon awakening. Such high levels would be contributed to ventilatory patterns during sleep, not to smoking. Many smokers have negligible levels after overnight deprivation. Since CO is a product of combustion, it cannot be employed in smokeless tobacco bioconfirmation. This measure is useful in the presence of NRT as it is specific to tobacco smoking and not nicotine. Higher CO levels are typically associated with higher daily smoking rates and can be used to biochemically validate self-reported cigarettes per day. With low levels of CO seen in light smokers, the CO measure is of marginal utility (Benowitz et al, 2002).

**Nicotine**

Nicotine can be measured in various biological specimens including saliva, urine, and plasma (Jacob & Byrd, 1999). Nicotine is readily absorbed by the lungs from cigarette smoke, is rapidly transported to the brain, and accumulates in the body during the day in regular users (Benowitz, Jacob, Denaro, & Jenkins, 1991). Nicotine has a short half-life of approximately two hours (Benowitz & Jacob, 1994; Benowitz, Jacob, Denaro, & Jenkins, 1991). Thus, it is inadequate in assessing tobacco use that occurred 8-12 hours previously. Plasma specimens avoid any contamination of oral nicotine in saliva samples. Plasma nicotine levels measured after smoking one cigarette range from 5 to 30 ng/ml. The sensitivity and specificity of plasma nicotine approximate 90% (Benowitz & Jacob, 1994). Nicotine levels can be obtained through methods of gas chromatography, immunoassays, or high performance liquid chromatography and are expensive. It is highly specific for tobacco use. In the absence of nicotine replacement therapy (NRT), plasma levels correlate well with nicotine intake and can estimate tobacco usage.
Samples taken in the afternoon of a smoking day are most correlated with intake. Due to nicotine’s short half-life and need for invasive blood sampling, plasma nicotine has not been widely used to verify tobacco use.

**Cotinine**

Cotinine is a major metabolite of nicotine and can be measured in plasma, saliva, and urine (Davis & Curvall, 1999). Plasma and saliva cotinine perform best with 96-97% sensitivity and 99-100% specificity (Jarvis, et al., 1987). Plasma cotinine has a disadvantage in that it requires the invasive procedure of a venipuncture. Cotinine levels peak in the body one to two hours after the last dose of nicotine. The main advantage of cotinine as a biochemical marker is its longer half-life indicating tobacco use over the past several days. The half-life of cotinine in the general population is 16 hours (Benowitz, et al., 2002). However, special populations metabolize cotinine differently. African-Americans and Chinese-Americans metabolize cotinine more slowly with a longer half-life of 20 hours for each population (Benowitz & Jacob, 1994; Ahijevych & Parsley, 1999). In contrast, pregnant women metabolize cotinine more quickly with a shorter cotinine half-life of 9 hours (Klebanoff, et al., 1998). The half-life must be considered when specimens are measured to obtain smoking status. To avoid false positive results, one must consider the longest cotinine half-life and typical initial cotinine levels. In addition, false positive results may be seen in individuals who have quit for two or more days before cotinine measurement. Thus, 7 days is a reasonable interval to use to assess compliance with non-smoking status (Benowitz, et al., 2002).

The cutpoints to differentiate smoking from non-smoking status for plasma or saliva cotinine is 15 ng/ml (Glasgow, et al., 1993). In pregnant women, the cut point is 10
ng/ml (Benowitz, et al. 2002) while the cutpoint for urinary cotinine is 50 ng/ml. A typical level of cotinine in a daily smoker is 300 ng/ml (Glasgow, et al., 1993). When smokers are categorized as light, moderate, or heavy smokers, cotinine levels are correlated with the level of smoking; however, there are no specific values established for these levels. A decrease in cotinine levels over time suggests lower smoking rates; cotinine could be a marker to validate harm reduction.

Smoking Cessation Pharmacotherapies

Although nicotine dependence is a chronic condition that often requires repeated intervention, there are effective treatments that can result in long term abstinence. The updated Clinical Practice Guideline (Fiore, et al., 2000) provides findings of meta-analyses of pharmacotherapy. Meta-analyses evaluated the effects of the selected pharmacotherapy compared to a placebo on abstinence from tobacco at endpoint of 5 months or longer. The studies met specified selection criteria of randomization of subjects to groups, at least 10 subjects in each arm of treatment, with outcome measures conducted at 5 months or longer after treatment. Based upon the meta-analysis, first-line pharmacotherapies have been identified (Fiore, et al., 2000) for treatment of tobacco dependence. These medications include NRT such as nicotine gum, nicotine inhaler, nicotine nasal spray, nicotine patch, and the medication bupropion sustained-release (BUP-SR). Subsequent to the 2000 Clinical Practice Guideline, the NRT lozenge was approved by the Food and Drug Administration; the lozenge has been shown to have similar effectiveness as other forms of NRT (Shiffman, Di Marino, Pilliteri, 2005; Shiffman, et al., 2002).
Nicotine Replacement Therapy

The pharmacology of action of the various forms of nicotine differs in the rate, site, and extent of absorption of the drug. Absorption is the most rapid with intranasal administration of the spray which has peak concentrations achieved within 4-15 minutes. Nicotine chewing gum peaks within 25-30 minutes while oral inhalation peaks within 15-30 minutes. The transdermal nicotine systems are slower with peaks occurring at 4-10 hours. Plasma nicotine concentration levels fluctuate least with the transdermal systems, and are least like those produced by cigarette smoking whereas the intranasal administration most closely mimics cigarette smoking (Fiore et al., 2000; American Society of Health Systems Pharmacists [ASHSP], 2006).

Nicotine Gum

The results of the meta-analysis of 13 studies that met inclusion criteria comparing nicotine gum to placebo (Fiore, et al., 2000) found that 2 mg nicotine gum improved long term abstinence rate by approximately 30-80 percent when compared to placebo. In addition, the 4 mg nicotine gum was associated with a higher abstinence rate in highly dependent smokers. These highly dependent smokers were defined as those who had experienced severe withdrawal during past quit attempts, smoked more than 25 cigarettes a day, and/or had the first cigarette of the day within 30 minutes after awakening.

Nicotine gum is available over-the-counter in a sugar-free, flavored chewing gum base as two mg or four mg squares. Gum is buffered to a pH 8.5 to enhance buccal absorption of the drug. Thus, acidic beverages such as coffee, soft drinks, and wine interfere with buccal absorption (ASHSP, 2006). Blood nicotine concentrations vary with use of
nicotine gum and depend upon the vigor and duration of chewing, amount of saliva produced while chewing, the amount of an extracted dose held in the mouth and accessible for buccal absorption as opposed to the amount expectorated or swallowed. Interestingly, nicotine gum may act as a substitute oral activity in behavior modification (Shiffman, et al., 2003). Patients should chew the gum slowly until a “peppery” taste appears. The gum is then “parked” between the cheek and gum to allow absorption through the oral mucosa. The “chew and park” for 30 minute pattern is followed until the taste disappears. To obtain the maximum benefit of nicotine gum, patients should be instructed to chew at least one piece of gum every one to two hours for at least one to three months (ASHSP, 2006; Fiore, et al., 2000; Hughes et al., 1999).

**Nicotine Inhaler**

The nicotine inhaler is an efficacious smoking cessation treatment as evidenced by four studies in the meta-analysis (Fiore et al., 2000) which found that the nicotine inhaler more than doubled long term abstinence rates when compared to a placebo inhaler. The inhaler is available only by prescription. After oral inhalation, nicotine is predominantly absorbed by the buccal mucosa. Approximately 20% of the inhaled dose of nicotine is swallowed; acidic beverages interfere with buccal absorption so only water should be consumed 15 minutes before and during inhalation. The delivery of nicotine from the inhaler is decreased in cold weather with temperatures below 40° F. A dose is considered a puff or inhalation from the nicotine inhaler. Each cartridge delivers a dosage of four mg of nicotine over 80 inhalations with a recommended dosage of 6-16 cartridges per day. The duration of therapy is up to six months with a tapering dose during the last three months of treatment (Fiore, et al., 2000).
Nicotine Nasal Spray

Nicotine nasal spray is also a first-line medication to treat tobacco dependence. Three studies met inclusion criteria for the meta-analysis (Fiore, et al., 2000) and found that when compared to a placebo spray, nicotine nasal spray more than doubled long term abstinence rates. Intranasal nicotine is rapidly absorbed and produces plasma concentrations similar to those of cigarette smoking. A dose of nicotine nasal spray is 0.5 mg to each nostril. Initial administration should be one to two doses per hour and can be increased for relief of symptoms. After administration of two sprays (1 mg of nicotine) almost 53% of the dose is systemically absorbed. The recommended minimum treatment is eight doses per day with the maximum limit of 40 doses per day. The duration of treatment is recommended to be three to six months (Fiore et al., 2000; Bansal, Cummings, Hyland, & Giovino, 2004).

Nicotine Patch

The nicotine patch is a first-line smoking cessation treatment. The results of 27 studies in the meta-analysis (Fiore et al., 2000) found that the nicotine patch approximately doubled long term abstinence rates when compared with placebo. After initial application of the patch or transdermal system of nicotine, a depot of nicotine is apparently formed in the skin beneath the patch. Plasma nicotine concentrations from the transdermal system increase slowly and peak four to ten hours after application. Plasma concentration levels decline slowly, which is reportedly related to the slow release of nicotine from the transdermal system. Plasma level concentrations remain steady with sequential application of the patches after two to four days. The patches are available as 7
to 21 mg per 24 hours and as 15 mg per 16 hours. A suggested schedule of usage for the 24 hour patch is 21 mg/24 hours for four weeks, then 14 mg/24 hours for two weeks, then 7 mg/24 hours for two weeks. The 15 mg/24 hours is used for eight weeks. The duration of treatment of eight weeks or less has been shown to be as efficacious as longer treatment periods (Fiore, et al., 2000).

**Nicotine Lozenge**

A NRT lozenge was approved by the Food and Drug Administration in 2002 for over-the-counter sale. The NRT lozenge is available in 2mg and 4mg strength. In contrast to other NRT therapies which use the amount of daily cigarettes smoked to select dosage, the lozenge uses the individual’s time to first cigarette. Since smokers awake in a state of nicotine deprivation, the time to first cigarette or the drive to self-administer nicotine is a strong indicator of nicotine dependence. Smokers who have their first cigarette of the day within 30 minutes of wakening should use a 4 mg dose while those having their first cigarette more than 30 minutes after wakening should use the 2mg lozenge. During the first six weeks of therapy, one lozenge is used every 1-2 hours; at weeks 7-9, one lozenge is used every 2-4 hours, and at weeks 10-12, one lozenge is used every 4-8 hours and then stopped. The nicotine lozenge releases nicotine as it dissolves in the mouth. The lozenge should remain in the mouth until it dissolves; it should not be bitten, chewed, or swallowed. Fifteen minutes should elapse after using the lozenge before one eats or drinks (ASHSP, 2006; Shiffman, Di Marino, & Pilliteri, 2005).

**Bupropion Sustained-Release**

Bupropion sustained-release tablet is a first-line non-nicotine medication indicated for treatment of tobacco dependence. The precise mechanism of action by which BUP-SR
enhances the ability of persons to abstain from smoking is not known (ASHSP, 2006). However, its mechanism of action is presumed to block neural re-uptake of dopamine and/or norepinephrine. This action is similar to the neurochemical effects of nicotine, which include the release of norepinephrine and dopamine in the brain. The dopamine and nonadrenergic effects of BUP-SR could be responsible for its smoking cessation efficacy (Hurt et al., 1997). The meta-analysis of two large multicenter studies (Fiore, et al., 2000) comparing BUP-SR to placebo found that BUP-SR approximately doubled long term abstinence rates. Patients are prescribed a dose of 150 mg every morning for three days, then increased to 150 mg twice a day. This dosing may continue for 7-12 weeks following the quit date. Patients initiate BUP-SR treatment while they are still smoking since steady-state plasma concentrations are not achieved until approximately one week after beginning treatment. The quit date should be scheduled within the first two weeks of BUP-SR therapy (Fiore, et al., 2000).

Selecting a Pharmacotherapy

Since the pharmacotherapy meta-analyses compared specific pharmacotherapies with placebo controls in each study, it is inappropriate to compare results of one medication with another (Fiore, et al., 2000). Selection of a specific pharmacotherapy considers preference of an over the counter intervention versus a prescriptive item, costs and available insurance coverage, preferred mode of administration, any contraindications to interventions, and undesired side effects of a specific route. Healthcare providers can increase their patient’s chances of cessation by discussing use of pharmacotherapies. Brief physician advice of 5 minutes or less in a single visit had 2-10% cessation quit rates at 5 or more months; the use of pharmacotherapies approximately doubled those quit
rates (Fiore, et al., 2000). In a random telephone survey conducted in 2001 (Bansal, Cummings, Hyland, & Giovino, 2004), data revealed that smokers were misinformed about the health risks of nicotine and the safety and efficacy of nicotine medications. They also lacked knowledge on available medications helpful in promoting cessation. While almost all of the adult smokers in the survey had heard of the nicotine patch and gum, less than 50% had heard of the inhaler and less than 10% had heard of the nasal spray; approximately 60% had heard of BUP-SR. The lack of knowledge of medication availability and/or misperceptions contribute to decreased pharmacotherapy use in cessation attempts.

**NRT Studies in Smokers with Schizophrenia**

As smoking rates in the general population decline, the percent of those who remain smokers will likely be psychiatric patients particularly those with schizophrenia. Yet, research has been limited in this special population. The use of pharmacological therapy intervention to decrease smoking and promote cessation has shown promising results in persons with schizophrenia. While studies initially focused on NRT, predominantly the patch, bupropion use has been studied more recently.

The use of the NRT patch has been effective in leading to abstinence in several studies of persons with schizophrenia. The study of Ziedonis and George (1997) found that after 10-weeks of psychosocial treatment either in group (focused on triggers, coping, and relapse) or individual motivational enhancement therapy (focused on motivation and commitment to change) with each subject using NRT patch, 40% (n=10) of the subjects (n=24) had reduced their smoking as measured by CO levels by 50% at the end of the trial. Thirteen (56%) of the 24 subjects were abstinent at a 6-month follow-up.
Abstinence status was confirmed by CO levels. In a sample of 50 smokers with schizophrenia, Addington and colleagues (1998) reported a 42% cessation rate at the end of a modified smoking cessation 7-week program; cessation rates dropped to 16% at 3 months, and 12% at 6 months. The NRT patch was offered to all subjects; forty subjects chose to use the patch which was given for 6 weeks and then tapered. All but one of the subjects who quit had used the NRT patch. In addition, those who attended the complete 7-week program remained abstinent at three month (n=8) and six month (n=6) follow-ups. Abstinence was confirmed by use of urinary cotinine levels.

In a convenience sample (n=10), subjects chose their type of pharmacotherapy and were scheduled to attend 10 weekly sessions on cessation information (Van Dongen, Kriz, Fox, & Hague, 1999). In this one-group design, four subjects were on NRT patch; one subject selected NRT gum; four were on BUP-SR, and one was on BUP-SR and NRT patch combined. Seven completed the program. At the end of the trial, the abstinence rate was 10% (n=1). One subject on NRT gum was abstinent while two with NRT patch, two with BUP-SR, and one with a combination of NRT patch and BUP-SR decreased their intake by 1/2 -1 pack per day; one with NRT patch had no significant differences in CO level from pre and post sessions.

One study was done where smokers with schizophrenia could smoke ad libitum with NRT patch to observe for effects of down regulation. Using a double blind, placebo-controlled, within subject crossover design, Dalack and Meador-Woodruff (1999) found that the NRT patch was effective in down regulation of smoking in a group (n=10) of heavy smokers with schizophrenia. When subjects smoked ad libitum during the 32 hour study period; mean expired carbon monoxide (CO) decreased by 15% with NRT patch
versus placebo. Nicotine plasma levels from smoking and NRT patch treatment were less
than those of smoking and placebo patch treatment again suggesting down regulation.

The dimension of the type of antipsychotic medication being used to treat
schizophrenia was added in 2000 (George, et al.). Smoking differences were being
observed as atypical antipsychotics began replacing the typical antipsychotics. The
differential effects of typical and atypical antipsychotic medications in enhancing
smoking reduction/abstinence rates may be explained through the reduction of a common
side effect known as akathisia associated with atypical antipsychotics (George et al.,
2000). Akathisia is characterized motor restlessness, ranging from anxiety to inability to
lie or sit quietly, or to sleep (Dorlands, 2004). In effect, both atypical antipsychotics and
nicotine have in common the ability to decrease antipsychotic-induced akathisia. When
this need is met by the medication, the need to obtain the same effect from nicotine is
lessened, and smoking is decreased. Akathisia with its inner feeling of restlessness may
inhibit the comprehension by the smoker on typical antipsychotics. The activity of
smoking also provides some purposeful movement in these smokers who have a need for
continual movement and restlessness.

Both nicotine and atypical antipsychotics induce the release of dopamine.
Schizophrenia is associated with deficits in prefrontal cortical dopamine. Bupropion also
augments the hypofunctional prefrontal cortical dopamine found in schizophrenia. Thus,
it may be more effective in smoking reduction/abstinence than NRT due to its action and
noted effects of reducing negative schizophrenia symptoms. Those taking typical
antipsychotics are believed to experience greater reward from smoking due to its action
on the postsynaptic dopamine receptors which mediates the reward system.
George and colleagues (2000) conducted a study of 12 weeks with subjects assigned to either American Lung Association program or to a specialized smoking cessation program with use of NRT patch in all subjects found a statistically significant difference in reduction of expired CO in patients treated with atypical (n=18) versus typical (n=27) antipsychotic medication. While the atypical antipsychotic clozapine has been associated with reduced smoking consumption in smokers with schizophrenia (McEvoy, Freudenreich, & Wilson, 1999), this study suggested a differential effect of other atypical medications (risperidone, olanzapine, and quetiapine) in improving smoking abstinence rates with the NRT patch. Significant attrition during the treatment phase was noted with those on typical antipsychotics completing an average of 7.3 weeks while those on atypical antipsychotics completed an average of 10.3 weeks. At a 6-month follow-up, three of the seventeen (17.6%) in the American Lung Association program and three of the twenty-eight (10.7%) in a specialized smoking cessation program remained abstinent. Three of 18 (16.7%) on atypical antipsychotics and two of 27 (7.4%) on typical antipsychotics were abstinent at 6-month follow-up. Abstinence rates favored the American Lung Association group and the group treated with atypical antipsychotics.

McDermott (2004) conducted a retrospective chart review to evaluate a 5-week smoking cessation clinic consisting of psychological support and use of NRT patch (n=86). At post trial follow-up, 41% (n=35) had quit smoking as evidenced by CO levels of 6 ppm or less. When smoking reduction was analyzed, a total of 58% (n=50) had reduced their CO levels by at least 10 ppm and of these 10% (n=9) had reduced their CO levels by at least 40 ppm. Carbon monoxide levels were obtained before and after NRT patch therapy or at weeks 3 and 5 of the 5-week program. While the author did not state
the time of the sessions and obtained CO readings, the sessions appeared to be scheduled at the same time each week. Variance in the time of day of CO monitoring could impact results due to short half-life of CO.

Since NRT nasal spray closely mimics the effects of smoking by providing rapid pulsatile nicotine delivery, its effectiveness in smokers with schizophrenia was explored by Williams, Ziedonis, & Foulds (2004). All subjects (n=12) received monthly individual psychosocial treatment for tobacco dependence and 8 attended additional group therapy sessions. Five subjects (42%) were abstinent for more than 90 days and had substantial reduction in expired CO levels from $21 \pm 2.6$ to $3.5\pm1.9$ppm. Increased use of the spray seemed correlated with abstinence. Three of the five (60%) who were continuously abstinent used the maximum recommended dosage of 40 doses a day.

Short term contingent monetary reinforcement for CO levels $\leq 11$ppm was shown to be effective in reducing smoking by persons with schizophrenia (Tidey, O’Neill, & Higgins, 2002). A within-subjects (n=14), repeated measures design consisted of three experimental conditions of contingent reinforcement with NRT patch, contingent reinforcement with placebo, and noncontingent reinforcement with placebo. Average CO levels were significantly higher in the noncontingent condition than in either of the contingent conditions using NRT patch or placebo. The use of NRT patch did not enhance that effect. Salivary nicotine levels were similar to each other and higher in the noncontingent and combination of contingent with NRT patch conditions than in the combined contingent and placebo condition. It was noted that the contingent and NRT patch condition reflected both the nicotine of the patch and the amount smoked. The results from the trial period were not sustained as follow-up results at two weeks after the
study’s completion found that the subjects’ average CO levels were not significantly different from those at baseline.

In conclusion, eight studies were reviewed related to use of NRT in smokers with schizophrenia. One study focused on effectiveness of contingent rewards based on CO levels. Of the other seven studies, six incorporated information on smoking cessation from 7 to 12 weeks and one study provided monthly sessions with some individual sessions. Six of the studies used NRT patch; one used NRT nasal spray, and one used a combination of therapies. The sample sizes varied with four studies having 14 or fewer subjects; one study had 24; two studies had 45-50 subjects, and one retrospective study had 86 subjects. The biological measure of CO was used at the end of each trial; six studies reported decreased CO levels at the end of the trial varying from 15 to 58% while two studies reported abstinence with rates of 10 to 40%. Two studies provided results only at the end of the study; one followed up at 2 weeks, and three provided 6-month follow-ups. One study followed subjects for 1 ½ years. Results of the end of the trials did not persist through the 6-month follow-ups which showed fewer subjects (10-54%) maintaining reduced CO levels.

Studies Using BUP-SR in Smokers with Schizophrenia

The antidepressant BUP-SR was initially shown to be effective for treatment of nicotine dependence in nonpsychiatric smokers (Hurt et al, 1997; Jorenby et al, 1999). An initial case report by Evins and Tisdale (1999) suggested the efficacy of BUP-SR in reducing cigarette smoking in schizophrenia patients. Weiner and colleagues (2001) found that CO was significantly decreased in 8 smokers with schizophrenia over 14 weeks of BUP-SR therapy combined with supportive therapy; no smoker achieved
abstinence at 14 weeks. In the first placebo study (n=18), a double-blind, placebo controlled study (Evins, et al., 2001) of BUP-SR with a dose of 150 mg daily and concurrent cognitive behavioral therapy, BUP-SR treatment was associated with greater reduction in mean CO by 30% in 6 of the 9 active treatment subjects at the end of the trial of 12 weeks. The study’s low dose of 150 mg BUP-SR was found to be safe and effective for smoking reduction, but not abstinence. The researchers noted a high rate of refusals for blood draws making cotinine assessments difficult, requiring use of CO to validate self-reported smoking status. At 12 weeks, they reported that the serum cotinine was reduced approximately 30% in the BUP-SR group, but increased in the placebo group approximately 10%. Subjects on atypical antipsychotics and BUP-SR had greater reduction in CO than subjects on typical antipsychotics or those on a combination of typical and atypical antipsychotics. At 6-month follow-up, one BUP-SR subject, but no placebo subject, achieved sustained abstinence from smoking. The placebo group did not experience any significant reduction in CO at any time point. Improvement in negative schizophrenia symptoms and greater stability of depression symptoms were noted in the BUP-SR group compared to placebo.

A 2-year follow-up (Evins, et al., 2004) was conducted with the subjects in the study of 2001 (Evins, Mays, Tisdale, Cather, & Goff). Seventeen of the 18 subjects completed follow-up assessments; one subject was lost to the study and was considered to be a smoker. The mean expired CO for the entire group was lower at 2 years than at baseline; individual reduced CO level at the end of the trial correlated significantly with reduction at 2 years. Those who had significantly reduced smoking at the end of the trial were more likely to have quit at two years than those who did not significantly reduce smoking.
during the trial. Six of 7 who had achieved significant reduction at the end of the trial had maintained reduction in smoking by 50% or more. Four of 18 were abstinent at 2 years follow-up; two of the four had received BUP-SR in the trial. Interestingly, 11 of the 18 had used pharmacotherapy between the end of the trial and the 2-year follow-up with nine using BUP-SR and two using NRT. At the 2-year follow-up, there was no difference in smoking behavior between those taking atypical and typical antipsychotics.

In a 10-week double-blind placebo controlled trial (n=32) of BUP-SR combined with weekly group therapy sessions with two groups of 16 each (George, et al., 2002), the 7-day point prevalence abstinence with CO bioconfirmation was significantly different when measured in week 10 with 50% (n=8) of the bupropion and 12% of the placebo group (n=2) achieving trial end-point smoking abstinence. At 6-month follow-up, there was no statistical difference in the groups. BUP-SR significantly reduced CO levels compared with placebo over the 10 weeks of treatment; however, from a subset of 16 subjects, BUP-SR nonsignificantly reduced plasma cotinine levels compared to placebo group at weeks 1, 4, and 10. Smokers treated with BUP-SR who were on atypical antipsychotic medication had significantly enhanced smoking cessation outcomes (8 of 12 subjects or 67%) compared to those on atypical medication and placebo (2 of 10 subjects or 20%) or those on typical antipsychotics and BUP-SR (0 of 4 subjects or 0%) or those on typical antipsychotics and placebo (0 of 6 subjects or 0%). Similar to the study of Evins and colleagues (2001), negative symptoms of schizophrenia were significantly reduced in the BUP-SR group compared to placebo and interaction of BUP-SR and atypical antipsychotics favored cessation outcomes.
In another study, Evins and colleagues (2005) found similar results of those by George et al. (2002). Subjects with BUP-SR treatment (n=25) were significantly more likely than the placebo group (n=28) to be abstinent at a 7-day prevalence point at 1-week post the quit date (day 15) and at the end of the intervention at week 12. They also had a significantly higher rate of 4-week continuous abstinence and a longer duration of abstinence. As in their earlier study (Evins, et al., 2001), there was a trend toward improvement in depressive and negative symptoms of schizophrenia.

In conclusion, in three of the five BUP-SR studies, a double blind placebo controlled study design was used with the number of subjects ranging from 18 to 53. All studies had subjects who expressed desires to quit smoking. Each study utilized specialized smoking cessation programs of 10-14 weeks and set a specific quit date between weeks three and four. Four used 300mg of BUP-SR daily while one study (Evins, et al., 2001) used 150mg daily. Outcome measures of CO levels were obtained at quit day and at the end of each study; two studies did a 6-month follow-up while one study had a 2-year follow-up. At the end of each study, BUP-SR subjects had reduced CO levels. The BUP-SR subjects were more likely to be abstinent at the end of the study and at the 6-month follow-up. In three studies, subjects experienced an improvement in depressive and negative schizophrenia symptoms. During quitting attempt, placebo subjects in Evins’ study (2001) had significant worsening in psychotic and depressive symptoms. Limitations of the studies were small sample sizes and low power in the results. There was no objective measure of medication compliance in any study.
Summary, Conclusion, and Next Steps

Biochemical verification of self-reported smoking status was present in each of the studies. Carbon monoxide was used in 6 of the 8 studies using NRT and in all BUP-SR studies. The collection times of CO samples were not consistently noted in the studies; since CO levels are time sensitive for accurate readings due to its short half-life, collection time is critical. One of the NRT studies used salivary nicotine. A problem with salivary nicotine is that results can be impacted by sample contamination of oral nicotine. Another NRT study used urinary cotinine. Neither salivary nicotine nor urinary cotinine data were reported in those NRT studies. Plasma cotinine was used in two of the BUP-SR studies; refusals for blood draws by the subjects contributed to a need to use either subsets for data analysis or reliance on CO data. Difficulty in obtaining plasma cotinine samples may be due to its disadvantage of requiring an invasive procedure of a venipuncture. There is a need to increase the use of the biomarker cotinine to validate harm reduction in this population of heavy smokers. Salivary cotinine collections are an alternative to plasma collections.

Nicotine replacement therapy patch combined with cessation programs or specialized therapy group sessions for smokers with schizophrenia having an interest in quitting have approached cessation rates as high as 40% at the end of trials lasting from 5-14 weeks. However, in those who have conducted 6-month follow-ups, the abstinence rates have decreased to as low as 12%. This may be largely due to the study medications being provided for the duration of the trials. Varied smoking cessation programs were not related to significantly greater cessation. Program approaches utilized standardized cessation programs, modified cessation programs for schizophrenia, specialized
psychoeducation groups, and motivational enhancement therapy. One study noted that NRT patch and cessation sessions with those on atypical antipsychotics had greater cessation at trial end and at 6-month follow-up than those on typical antipsychotics. Use of NRT spray at higher dosage of 40 sprays per day was associated with lower CO levels and longer abstinence rates than lower spray dosages.

When NRT patch was used in smokers who were not trying to quit, there was a reduction in CO levels compared to placebo, but it was not significant. When monetary incentive was provided based upon CO levels, the contingent monetary conditions reduced smoking in both NRT patch and placebo subjects; however, the NRT patch had no significant effect compared to placebo on reducing the amount smoked as measured by CO levels. The contingent monetary awards were effective during the study, but did not persist at a 2-week follow-up.

Fewer studies have been conducted with BUP-SR and the schizophrenia population who smoke. The four studies in this paper included subjects who desired to quit smoking and all received some type of smoking cessation program ranging from 10-14 weeks. Those on BUP-SR in all studies had significant reductions in CO levels at the end of the trials and at 6-month follow-up in two studies. One study utilized a low dose of BUP-SR which may have limited success of lowering CO levels and cessation. While there was some reduction and abstinence in the subjects with placebos at the end of the trials, it was not significant. The use of BUP-SR was associated with improvement in depressive and negative symptoms. The 2-year follow-up of Evins and colleagues (2004) is promising in that smokers with schizophrenia interested in quitting continued to seek assistance and pharmacotherapy to quit. This group’s success mimics the general population. Smokers
usually need several attempts, sometimes as many as 8-10 attempts, before being able to maintain cessation (American Cancer Society, 2006). While 46% of smokers try to quit each year, only about 7% are abstinent at 1 year, representing a relapse of about 85% (Fiore, et al., 2000). Garvey and associates (1992) estimate that 60-90% of smokers who quit will relapse within 1 year. Little is known about relapse after 2 or more years of abstinence. In a study (Krall, Garvey, & Garcia, 2002) of 483 men receiving care in a Veterans Healthcare System, 93 subjects (19%) eventually relapsed after 2 or more years of abstinence with relapse fluctuating between 2-4% in the second to sixth year after abstinence to less than 1% after 10 years of abstinence.

These outcomes occurred in conjunction with the studies’ varied smoking cessation information strategies. No significant differences in outcomes were found with use of these varied approaches. While the smoker with schizophrenia may have the same learning needs as others who are seeking ways to quit and may benefit from either a standard or modified program, the basic nature of schizophrenia may decrease their tolerance to a large amount of information and rigid formats typical of community-based smoking cessation programs.

Since smoking alters the metabolism of psychotropic drugs, clinicians must consider this factor in prescribing medications when these patients attempt cessation or require hospitalization in smoke-free environments. Larger, extended trials are warranted to assess if smoking levels can be reduced in this population and if this can lead to smoking cessation. For those who are not interested in cessation or cannot achieve cessation, reducing the health risks associated with tobacco usage may be a sensible response (Institute of Medicine, 2001). Studies have shown an interest in not only cessation but in
Reducing tobacco usage as evidenced by reporting of reductions in CO, nicotine, and cotinine levels. This is an alternate outcome that may contribute to improved health outcomes and decreased comorbidities in this population.

Quitting smoking and maintaining abstinence is a lengthy process for those with schizophrenia. Relapses are common; quitting is difficult, but not impossible. Giving up smoking requires a change in lifestyle which may be especially difficult for those with schizophrenia. Clinicians must use every opportunity to counsel patients on effects of smoking, benefits of quitting, and discuss available pharmacotherapy options.
LIST OF REFERENCES


CHAPTER 3

BIOBEHAVIORAL NICOTINE DEPENDENCE IN PERSONS WITH SCHIZOPHRENIA

Introduction

Tobacco use continues to be the single greatest preventable cause of morbidity and mortality in the United States and is responsible for more than 440,000 premature deaths annually (United States Public Health Service [USPHS], 2005). Smoking contributes to several chronic diseases and consequently produces staggering health-related economic costs to society, approaching $167 billion annually (USPHS, 2005). While the prevalence of smoking by adults in the United States has declined to approximately 20.9% (Centers for Disease Control, 2005), smoking remains extremely common among those with psychiatric disorders. It has been estimated that persons with a diagnosable mental disorder in the past month consume nearly half of all cigarettes smoked in the United States (Lasser, et al., 2000). The prevalence of current smoking in persons with schizophrenia has been reported as high as 88% (Lohr & Flynn, 1992). In another study, de Leon and associates (2002) found that the prevalence of ever and currently daily smoking for patients with schizophrenia was 92% and 83% respectively; prevalence for patients with mood disorders was 78% and 65%, and prevalence for controls was 47% and 26%.
Persons with schizophrenia were more likely to be heavy smokers defined as smoking more than 1½ packs a day (Lohr & Flynn, 1992). Over half of the persons with schizophrenia smoked high tar cigarettes in contrast to less than 1% of the general population (O’Farrell, Connors, & Pepper, 1983), and they often smoked most of the cigarette tobacco rod containing higher levels of nicotine, thus increasing reinforcement of this behavior (O’Farrell, et al., 1983). In a population-based smoking study, 40% of those without mental illness who had ever smoked daily for one month or more had quit, while none of the smokers with schizophrenia had quit (Lasser, et al., 2000).

A variety of factors have been attributed to their inabilities to quit smoking. Some of these are specific to the effects of nicotine itself. Nicotine is thought to interact with many of the same aberrant pathways in schizophrenia thus impacting on the negative and positive symptoms of schizophrenia. Schizophrenic patients use nicotine to self-medicate negative symptoms of amotivation, dysfunctional relationships, and affective blunting (Ziedonis, kosten, Glazer, & Frances, 1994) or to transiently improve attention and memory (Smith, Singh, Infante, Khandat, & Kloos, 2002). Schizophrenia is associated with difficulty in processing sensory information. Nicotine has the ability to temporarily normalize sensory gating and thus decreases difficulty with processing sensory information (Adler, Lee, Hoffer, Wiser, & Freedman, 1993). Persons with schizophrenia also may smoke to alleviate the extrapyramidal side effects of psychotropic medications (Lohr & Flynn, 1992). Smoking increases the metabolism of psychotropic medications and patients with schizophrenia who smoke receive higher doses of neuroleptics than non-smokers (Ziedonis, Kosten, Glazer, & Frances, 1994).
Schizophrenia is rare in children; its average age of onset is 18 years old in men and 25 in women (World Health Organization, 2001). Interestingly, the age of onset of schizophrenia parallels that of initiation of daily smoking and nicotine dependence. In a study with a sample of patients with schizophrenia (n=66), patients with a mood disorder (n=51), and a control group of community subjects (n=404), smoking initiation before the age of 20 years was similar across the groups (de Leon et al., 2002). However, after the age of 20 years, the initiation of daily smoking in those with schizophrenia was higher than in those with mood disorders or the control group. The association between schizophrenia and higher risk of initiating daily smoking after 20 years of age may be consistent across countries (Gurpegui, et al., 2005). In their study conducted in Spain, smoking initiation rate after the age of 20 years was significantly different with a higher rate occurring in patients with schizophrenia (n=250) than in the control group (n=290). This lends more support to the earlier discussion of the use of nicotine as a means to self-medicate in this population.

Schizophrenia is a debilitating disorder of the central nervous system. The complexity of the underlying pathophysiology of schizophrenia is not completely understood. While decades of research have focused on singular importance of dopamine and dopamine receptors, other neurotransmitters and their role in the complex neurocircuity in schizophrenia have been identified, including serotonin, and cholinergic and glutamatergic neurotransmitters (Spollen, 2002). Antipsychotic medications are used to treat schizophrenia; these are classified as typical and atypical antipsychotics. The mechanisms of action differ in the typical and atypical antipsychotic medications, but
both target the brain’s dopamine D₂ receptor. The typical antipsychotics bind more tightly to the dopamine D₂ receptor than dopamine itself and have dissociation constants that are lower than that for dopamine. The atypical antipsychotics bind more loosely to the dopamine D₂ receptor than dopamine itself and have dissociation constants higher than that for dopamine. Radioactive typical antipsychotics dissociate very slowly over a 30-minute time span while radioactive atypical antipsychotics dissociate rapidly in less than 60 seconds. This transient occupation of dopamine D₂ receptors with rapid dissociation allows for normal dopamine neurotransmissions, keeping prolactin levels normal, sparing cognition, and minimizing extrapyramidal symptoms (Seeman, 2002).

Unlike typical antipsychotics, atypical antipsychotic medications are believed to block 5-HT₂A (serotonin) receptors at the same time as they block dopamine receptors (Kinon & Lieberman, 1996; Seeman, 2002). Blocking 5-HT₂A receptors increases the release of dopamine to such an extent that some of the D₂ blockade of the antipsychotic is reversed (Casey, 1995).

The typical antipsychotic medications used to treat schizophrenia are highly effective, but are associated with severe extrapyramidal side effects, predominantly dystonia, parkinsonian-like syndrome, and tardive dyskinesia. These side effects are a major concern as the medication that treats persons with schizophrenia leaves them with life long disabilities. Atypical antipsychotic medications which were introduced in the 1990’s seemed to have the same efficacy as typical antipsychotic medications but with minimal or no extrapyramidal side effects.
Pharmacotherapy for treating schizophrenia is a dynamic process as individuals can respond very differently to any particular medication (Leslie & Rosenheck, 2002). Overall, the use of atypical antipsychotic medications has grown; for example, 83.2% of veterans with schizophrenia receiving antipsychotic medications from the Veterans HealthCare System (n=76,787) were treated with atypical antipsychotic medication in 2005 (Leslie & Rosenheck, 2006). This is an increase of 24.4% from the 1999 data, the first year that these data were available. In 2005, only 9.3% were treated with multiple antipsychotic medications (Leslie & Rosenheck, 2006). Studies suggest that the atypical (ATYP) antipsychotic clozapine may reduce smoking in these patients (McEvoy, Freundenreich, & Wilson, 1999; Skogh, Bengtsson, & Nordin, 1999) while the use of the typical (TYP) antipsychotic haloperidol could increase cigarette smoking (McEvoy, et al., 1995). Additional factors contributing to increased smoking are social factors such as lower income and educational levels (Jarvis & Wardel, 2005; Ziedonis, Kosten, Glazer, & Frances, 1994). Other noted contributing factors were that persons with schizophrenia often have less access to interpersonal support and may be more likely to perceive their health as being out of their control (Holmberg & Kane, 1999).

Persons with schizophrenia smoke more intensely and thus self-administer more nicotine during cigarette smoking than non-schizophrenic smokers (Olincy, Young, & Freedman, 1997). The consumption of higher doses of nicotine was attributed to deeper inhalation. The average cotinine level of smokers with schizophrenia was 1.6 times higher than that of non-schizophrenia smokers who smoked a similar number of cigarettes a day (Olincy, et al., 1997). To assess whether smokers with schizophrenia had
different smoking patterns than non-schizophrenia smokers, Tidey and colleagues (2005) compared smoking topography measures in smokers with schizophrenia (n=20) to smokers without a psychiatric diagnosis (n=20). During a 90-minute *ad lib* smoking period, smokers with schizophrenia differed significantly with more total puffs per session and puffs per cigarette, shorter inter-puff intervals and larger total puff volumes, and carbon monoxide (CO) boost per session. The groups did not differ significantly on puff volume, puff duration, maximum velocity, or CO boost per cigarette. When TYP versus ATYP antipsychotic medications were compared, those on TYP antipsychotics smoked more cigarettes a day, had higher Fagerstrom scores for dependency, and greater CO boost per cigarette ratios.

Although smoking cessation is the ideal goal proposed to smokers by healthcare professionals, there are severely dependent smokers who are unable or unlikely to quit. These hard-core smokers have common social determinants including lower educational levels, lower incomes, and presence of mental health illnesses (Banks, Marmot, Oldfield, & Smith, 2006; Healton & Nelson, 2004; Hudson, 2005; Jarvis & Wardle, 2005). An alternative for these smokers may be a program of harm reduction (Jimenez-Ruiz, Kunze, & Fagerström, 1998; Zellweger, 2001). Reducing tobacco intake may decrease smoking-related risk factors associated with increased morbidity and mortality and may be a step toward cessation. While several studies have found that nicotine replacement therapy safely decreased smoking in the schizophrenia population (Addington, el-Guebaly, Campbell, Hodgins, & Addington, 1998; Dalack & Meador-Woodruff, 1999; George, et al., 2000; VanDongen, Kriz, Fox, & Hague, 1999; Williams, Ziedonis, & Foulks, 2004;
Ziedonis & George, 1997), fewer intervention studies have utilized bupropion despite preliminary studies suggesting efficacy of its ability to reduce daily smoking consumption in this population (Evins, et al., 2001; Evins & Tisdale, 1999; George, et al.; Weiner, 2002; Ball, Summerfelt, Gold, & Buchanan, 2001).

The effects of antipsychotic medications on smoking behaviors of those with schizophrenia have not been addressed extensively. These effects may be essential for understanding nicotine dependence in those with schizophrenia. Several studies suggest that persons on ATYP medications may have reduced smoking patterns (George, et al., 2002; McEvoy, Freudenreich, & Wilson, 1999; Skogh, et al., 1999; Tidey, et al., 2005). Therefore, the aims of this study were (1) to compare baseline smoking topography parameters, smoke constituent exposure, and levels of nicotine dependence in smokers with schizophrenia on ATYP and TYP antipsychotic medications, and (2) to compare smoking topography parameters, smoke constituent exposure, and levels of nicotine dependence in smokers with schizophrenia on ATYP and TYP antipsychotic medication during eight weeks of bupropion therapy. Comparisons were made at two, four, and eight weeks after initiation of bupropion therapy.

Method

Design

A repeated measures design was instituted. A sample of subjects over the age of 18 with a diagnosis of schizophrenia was recruited with the type of antipsychotic medication as the stratifying factor of ATYP versus TYP medication category. This was a one
between and four within repeated measures design. All subjects were exposed to the
treatment condition and all had repeated measures.

Participants

Forty-eight male smokers and one female smoker with schizophrenia or
schizoaffective disorder were recruited using flyers placed in a local Veterans Affairs
Medical Center and by face-to-face contact with research assistants. All participants were
recruited from supervised community group homes, and were required to be at least 18
years of age, with a self-report of smoking daily for the last six months, and met DSM-IV
(American Psychiatric Association, 1994) criteria for schizophrenia by chart review.
Potential participants were excluded if they were not legally competent to sign the
informed consent, could not answer correctly a 9-item comprehension questionnaire on
the important points of the study, or tested positive for pregnancy. Medical records were
reviewed and used to exclude those with seizure disorders, other substance use disorders,
or history of serious medical conditions. Potential participants were excluded if they had
not been on their current antipsychotic medications for at least two years, were on a
combination of TYP and ATYP antipsychotics, or had existing contraindications to the
study’s use of bupropion. Study procedures were approved by the institutional review
boards of the universities and medical center involved. Participants provided informed
consent and correctly answered all items of a comprehension protocol prior to
participating. Details of this process are provided elsewhere (Yerardi & Ahijevych, 2007,
in review). Out of the 129 patients who qualified for the study, 80 declined to participate.
Most declinations were related to not desiring to take another medication and not wanting to be a “guinea pig.”

**Procedures**

After providing informed consent and achieving 100% on the comprehension of consent form questionnaire, subjects were scheduled into the smoking protocol clinic. Each participant was asked to bring his/her usual brand of cigarette smoked, as smokers prefer a specific brand and smoking behavior may be altered if required to smoke an unfamiliar brand. The subject was acclimated to the environment and research staff. Familiar environmental cues such as magazines, ice water, and a television were available to increase comfort level. Acclimation included ways to promote the comfort of the subject such as introducing the staff, reviewing the study’s procedures for the visit, allowing the subject to select a television program or to read, providing ice water to drink, and assuming a comfortable position in the chair. Smoking protocols were conducted in an approved reverse ventilated private room in a medical center building. Four visits were scheduled during the study at baseline, and weeks two, four, and eight (Table 3.1).

Vital signs and weight were obtained at each visit along with self-reported questionnaires on nicotine dependence and smoking history. The Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991) was used to measure nicotine dependence with potential scores of 0 to 10 with a score of 7 or more reflecting very high nicotine dependence (Fagerström, Heatherton, & Kozlowski, 1991).
Medication Protocol

The informed consent provided information on the dosage, frequency, action and possible side effects of bupropion. A copy of the informed consent was given to each participant for future reference. In addition, at the time bupropion was dispensed from the pharmacy, both the participant and the supervising staff in the group home received medication instructions. Bupropion sustained-release tablets were prescribed at 150 mg daily for three days then 150 mg twice a day for the duration of the study. Each participant was instructed to begin bupropion the morning after the first clinic visit. Compliance to taking prescribed bupropion was confirmed by verbal feedback of the supervising staff responsible for oversight of medication in the group homes. Each participant received a $10 gift certificate at the conclusion of each visit attended, for a maximum of $40.

Measures

Smoke Constituent Measures

A structured timed protocol was implemented to facilitate consistent data collection across time and participants. Two minutes before each smoking bout and two minutes after smoking a cigarette, a carbon monoxide in expired air sample was obtained using a carbon monoxide monitor (Bedfont Mini-Smokerlyzer instrument; Innovative Marketing, Bedford, NJ). Subjects were instructed to hold their breath for 15 seconds then exhale into the disposable tube attached to the t-piece of the Smokerlyzer. The instrument was calibrated per manufacturer’s instructions with a 50 ppm CO standard. Drift is <1% of signal/month at constant temperature. The Smokerlyzer detects from 0-500 ppm CO with...
a digital display of the value thus eliminating observer error. The carbon monoxide boost was calculated by subtracting the pre-cigarette from the post-cigarette carbon monoxide levels. The carbon monoxide boost assessed level of smoking intensity during the smoking bout. Carbon monoxide boost was measured at each visit.

One minute prior to each smoking bout and one minute after smoking a cigarette, a blood sample of 4 ml was obtained for nicotine and cotinine analysis. An intravenous saline lock was used to avoid two separate venipunctures pre and post smoking. The saline lock also facilitated the timeliness of the withdrawal of the blood specimens since timing was critical for accurate calculation of nicotine boost by subtracting the level at one minute prior to smoking to the one minute post smoking of one cigarette. The plasma nicotine and cotinine levels were assayed by high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) at the Mayo Clinic (Moyer, et al., 2002). The LC-MS/MS method has correlations of variance for both intra-assays and inter-assays of nicotine and cotinine ranging from 4.9% to 11% with excellent correlations (r>0.98) to comparison methods (Moyer, et al., 2002). Plasma samples were obtained at each of the four visits.

**Smoking Topographic Measures**

Subjects smoked using the Clinical Research Support System (CReSS; Plowshare Technologies, Baltimore, MD), a widely used and reliable system for measuring smoking topography. The CReSS was calibrated prior to each smoking bout using a calibration syringe to create puffs of 30ml, 40ml, and 50ml ranges and adjusting the Scale Factor to accurately match the CReSS measurements with the syringe volume readings. CReSS
smoking topography results were a valid and reliable index of conventional smoking in the study by Lee and colleagues (2003) who found good reliability across a total of 48 smoking bouts with seven subjects over four days and 10 subjects over two days with correlation coefficients computed for puff volume at 0.66, puff duration at 0.75, and maximum puff velocity at 0.68. The ad lib mode was used in the current study allowing subjects to smoke a cigarette through a mouthpiece in their usual manner while topography measures were collected. This portable hand-held device calculates and stores numerous smoking topography measures, including time to smoke a cigarette, total number of puffs smoked per cigarette, total puff volume per cigarette, duration of inter-puff interval, puff volume, puff duration, and puff velocity. Data were recorded on the portable CReSS device and available only to study staff through a required log-on authorization process thus maintaining subject confidentiality and data integrity. A computer with a web browser was used to initialize and retrieve recorded data from the portable device (Plowshare Technologies, 2001). Smoking topography was measured at each visit. The butt length of each cigarette was measured in mm without the filter after each smoking bout. Participants were instructed to continue to smoke ad lib throughout the study. Each participant was scheduled into the study’s clinic at the same time throughout the study; these times varied from late morning to late afternoon. The time of the last cigarette smoked prior to the study’s cigarette was obtained.

Psychological Measures

Participants met with their healthcare provider on three of the four visits for assessments to review their tolerance to the treatment protocol. These standardized
assessment instruments were familiar to the participants with schizophrenia. Since bupropion was originally marketed as an antidepressant, depression was assessed for changes with the Montgomery-Asberg Depression Rating Scale (MADRS). The Positive and Negative Symptoms Scale for Schizophrenia (PANSS) and the Abnormal Involuntary Movement Scale (AIMS) were used to assess for any changes over time in symptoms. These instruments are briefly reviewed.

The MADRS, a 10 item rating scale to assess depression, was completed at baseline, week 4 (third visit) and at week 8 (fourth visit). Nine of the items are based upon patient report, and one is on the rater’s observation of the patients. Range of possible MADRS scores is 0-60 with higher scored indicating increased symptoms of schizophrenia. Since each of the 10 items on the MADRS is equally weighted, it is easy to follow and use (Khan, Khan, Shankles, & Pollissar, 2002). Less experienced raters reliably estimate accurate scores with MADRS because there are understandable anchors for each item (Khan, et al., 2002). Khan and associates (2004) found the MADRS to be as sensitive an instrument in detecting antidepressant efficacy in clinical trials as the Hamilton Depression rating scale with similar effect sizes (0.68 and 0.57 respectively; n=139). The MADRS does not focus predominately on the somatic symptoms of depression, but rather focuses on symptoms such as tension, sadness, pessimistic thoughts, lassitude, and suicidal thoughts. The MADRS is frequently used in medication therapy clinical trials to evaluate the effects of psychotropic medication on symptoms of depression (Sajatovic & Ramirez, 2001). The MADRS was completed at baseline, and at four and eight weeks by the study’s mental health care provider.
The PANSS, a 30 item rating scale specifically designed to assess individuals with schizophrenia, was completed at baseline, week four (third visit) and week eight (fourth visit). The PANSS consists of a semi-structured interview and available supporting clinical information. The PANSS is based upon the premise that schizophrenia has two distinct syndromes, a positive and a negative syndrome (Donaldson, Gelenberg, & Baldessarini, 1983). The positive syndrome includes productive features, such as delusions and hallucinations, while the negative syndrome includes those features which are lacking or poorly developed in individuals with schizophrenia, such as social withdrawal and flattened or blunted affect. There are 30 items which are rated along a seven point continuum (1=absent, 7=extreme) with a potential score ranging from 30-210. Higher scores reflect increased symptoms of schizophrenia. Alpha-coefficient analysis has indicated high internal reliability and homogeneity among PANSS items with coefficients ranging from 0.73-0.93 (p=.001) for each of the scales (Sajatovic & Ramirez, 2001). The PANSS was completed at baseline and at four and eight weeks of the study.

The AIMS is a 12-item instrument; 10 items are utilized to provide a numeric measure of the observed abnormal movements in different parts of the body; two non-scored items are related to dental status of problems with teeth/dentures and wearing of dentures. Poor dental status may exaggerate oral movements in some patients (Sachdev, 2000). Observed abnormal movements in the AIMS can be produced by a number of conditions including exposure to psychotropic medication such as may occur with tardive dyskinesia. The AIMS is heavily used in clinical trials evaluating new antipsychotic
medications. The AIMS information is collected after a brief neurological examination. This information is scored on a five-point scale (0=none, 4=severe) which evaluates abnormal movements using three subscales based on main anatomic areas of the orofacial area, extremities, and trunk. Potential scores range from 0-40 with higher scores indicating larger degree of extrapyramidal side effects. Experienced raters obtain higher levels of agreement compared to those who are less well-versed in using the scale (Sajatovic & Ramirez, 2001). The AIMS was completed at baseline and week eight (fourth visit) by the study’s physician.

Data Analysis

Descriptive analyses were conducted at baseline, and at two, four, and eight weeks on the variables of carbon monoxide and nicotine boosts from pre to post smoking of one cigarette, cotinine levels, FTND scores, and topography measures of number of puffs from each cigarette, puff volume, puff duration, interpuff interval, and total puff volume per cigarette. The comparisons of groups on ATYP and TYP medications at baseline were done with t-tests or nonparametric analyses with data not normally distributed. The second aim to differentiate smoking topography parameters, smoke constituent exposure, and levels of nicotine dependence for the ATYP and TYP medication categories at two, four, and eight weeks after bupropion therapy was initiated utilized repeated measures ANOVA to analyze changes within the individual over time and compare the two groups on the above variables. This was a one between and four within repeated measures design. Paired t-tests were done to compare variables at baseline and eight weeks for a given individual. A regression analysis was employed to examine possible predictors of
exposure. A power analysis with four repeated measures with an estimate of the average correlation of $r=0.50$ of the participants’ responses over time, and a large effect at the .05 level showed that 13 subjects were needed in each category (Stevens, 2002).

Results

Of the 49 subjects enrolled, 30 were on ATYP antipsychotic medications (clozaril, olanzapine, quetiapine, and respiradone) and 19 were on TYP antipsychotic medications (haloperidol and fluphenazine). At visit two, 20 participants on ATYP and 11 participants on TYP completed data collection; at visit three, 19 participants on ATYP and 10 participants on TYP participated; and at visit four, 16 participants on ATYP and 9 participants on TYP participated. The 25 participants who completed the study at eight weeks represented 53% of those on ATYP medications at baseline and 47% of those on TYP medications. The subjects who withdrew from the current study cited inconvenience in taking an extra medication or time demands of the four visits. Four subjects reported side effects of increased anxiety and nervousness; two of these subjects withdrew after two visits.

Demographic and baseline smoking characteristics of the total sample and participants on TYP (n=19) and ATYP (n=30) antipsychotics are shown in Table 3.2. There were no significant differences on demographic variables between the groups. None of the participants were employed either full or part time. While there were no significant differences in MADRS and PANSS scales at baseline, the positive, negative, and general subscales of the PANSS were slightly higher in the group on ATYP antipsychotics (ATYP Mean: 15.1±6.2 vs. TYP: 12.8±5.4; ATYP Mean: 15.2±5.3 vs.
MADRS scores were nonsignificantly higher as well (ATYP Mean: 7.9±6.9 vs. TYP: 6.0±7.1). Higher scores reflect higher levels of symptoms related to schizophrenia and depression. The orofacial and global judgment subscale scores of the AIMS were not significantly different by medication category. In addition, those on ATYP medications reported nonsignificantly fewer numbers of cigarettes smoked per day (ATYP Mean= 20.3±10.2 vs. TYP: 25.7±19.1).

No significant differences were found in either biological or topography measures by medication category at baseline (Table 3.3). Carbon monoxide levels of the 49 subjects at pre and post smoking and calculated CO boosts tended to be nonsignificantly higher in those with TYP medications. Nicotine and cotinine levels for 48 of the 49 participants were analyzed at baseline. One plasma sample leaked in shipment. This specimen was from a participant with only a baseline visit in the study and on a TYP antipsychotic medication. The nicotine and cotinine levels thus reflect a total of 18 participants on TYP medications and 30 on ATYP medications. Biological measures of nicotine and cotinine, carbon monoxide, and patterns of smoking topography were not significantly different in the two groups. Interestingly, nicotine boost approached significance (p=.06) with participants on ATYP medications higher than those on TYP medications (ATYP Mean= 23.9±14.4 ng/ml vs. TYP: 12.6±10.6 ng/ml). At baseline, the interpuff interval approached significance (p=.07) between the groups with those on TYP medications having shorter interpuff intervals (TYP Mean= 12.2±7.3 seconds vs.17.3±10.7 seconds).
To address the second research question, smoking topography parameters, smoke constituent exposure, and levels of nicotine dependence were analyzed for changes over time within and between ATYP and TYP medication groups. When the total number of subjects (n= 25 to 49) was reviewed for each visit, descriptively there were slight changes in both groups in topography and CO boost (Table 3.4). When comparing visit one data to visit four, small changes were noted in the way that the cigarette was smoked in both groups with increased mean flow, increased peak flow, and decreased number of puffs per cigarette. Nicotine and cotinine levels of total participants had an average cotinine value of 259.8±164.3 ng/ml at baseline (Table 3.5).

During eight weeks of bupropion therapy (Table 3.6; n=25), there were no significant differences within or between groups for puff volumes, time of peak flow, puffs per cigarette, duration of puffs, butt length, reported number smoked per day, or FTND scores. There were significant within subject differences over time on interpuff interval (p=.03; F=3.42), flow rate (p=.01; F=4.40), and peak flow (p=.01; F=4.71). Interpuff intervals shortened over time in the atypical medication group; mean flow and mean peak flow increased over time in both groups. There were some large standard deviations in the data reflective of noted variability within groups. The variance is a representation of natural phenomena as smokers differ. Carbon monoxide boost was significantly different between groups over time. Carbon monoxide boost decreased in those on ATYP antipsychotic medications, but remained the same in those on TYP antipsychotic medications.
Neither the PANSS scores nor the MADRS scores had any significant change over time within or between subjects at visits one, three, and four. When the two AIMS scores of visits one and four were analyzed with a paired t test, there were no significant differences over time within groups for any of the subscales of the orofacial, extremities, or global judgment nor the total AIMS score. These findings indicate no worsening of symptomology related to schizophrenia over time with bupropion use.

For those with data at all time points (n=25), there were no significant between group changes from visit one to visit four on either pre-cigarette or post-cigarette nicotine or cotinine levels and boosts (Table 3.7). Within group changes occurred from baseline to eight weeks on post-cigarette nicotine levels (p=.04) and post-cigarette cotinine levels (p=.07). Post-cigarette nicotine levels decreased from an average of 44.4±16.4 to 34.4±16.5 ng/ml in the group on ATYP antipsychotics and from an average of 35.7±15.6 to 31.9±12.3 ng/ml in the group on TYP antipsychotics. Post-cigarette cotinine levels decreased from an average of 294.9±160.5 to 225.9±157.3 ng/ml in the group on ATYP medications and from a mean of 335.4±129.3 to 303.0±163.7 ng/ml in the group on TYP antipsychotic medications. Since no significant between group differences were identified, the subgroup of 25 participants who completed all four visits were analyzed as a group. Paired samples Wilcoxon test for these 25 participants found within subject significant decreases over time for post-cigarette nicotine levels (p=.04; Table 3.8; Figure 3.1) and for post-cigarette cotinine levels (p=.01; Table 3.8; Figure 3.2).

Possible predictors of exposure were examined. In regression analysis, 18.5% of variance in tobacco use as indicated by pre-cigarette CO level was explained by pre-
cigarette cotinine level for 48 participants at baseline. At visit one, the interpuff interval accounted for 7.8% of variance in the post-cigarette CO level approaching significance at .052. For 25 subjects completing all four visits, variance in smoke exposure as indicated by post-cigarette CO levels at visit four was explained by cotinine of visit one (27.5%) and medication category (13.0%) for a total of 40.5% variance. Higher baseline cotinine levels and typical antipsychotic medication category were associated with increased CO exposure. To a lesser degree, variance in tobacco use as indicated by post-cigarette CO levels at visit four was explained by post-cigarette nicotine level at visit four (20.3%) and medication category (19.3%) for a total of 39.6%. Higher post-cigarette nicotine levels were associated with higher post-cigarette CO levels at the end of eight weeks. The TYP antipsychotic medication category was associated with higher post-cigarette CO levels.

Discussion

Characteristics of Sample

The aims of this study were to examine if persons with schizophrenia on atypical antipsychotics smoke differently than those on typical antipsychotics and how their smoking behaviors and exposure were affected over an eight-week bupropion treatment period. This smoking sample of persons with schizophrenia and their characteristics differ from those in previous studies which have enrolled predominantly outpatients in the community. The subjects in the current study resided in supervised residential settings. They have been unsuccessful at independent living, need assistance with items such as meals and keeping appointments, and have the financial resources for the housing. Some of these individuals are incompetent to handle their own funds and/or
make their own decisions and have appointed guardians. This contributed to the challenge of recruiting study subjects who could provide their own informed consent and answer correctly all comprehension questionnaire items as part of informed consent.

The attrition rate of approximately 50% in this eight-week study was higher than in most other studies. Other studies using bupropion with persons who have schizophrenia were 10-14 weeks in length (Evins, et al., 2001; Evins et al., 2005; George et al., 2002, and Weiner et al., 2001); however, they included weekly smoking cessation sessions thus providing more frequent contact with the subjects. The subjects in the current study received routine appointment notification consisting of a letter and a telephone call. Another potential explanation for the higher attrition may be that these participants were sicker. The severity of schizophrenia in the current study’s participants is reflected in employment status as none of them worked either full or part time. Other studies have reported low rates of employment ranging from 5-15% for persons with schizophrenia (Tidey, et al., 2005). Compliance with taking bupropion as prescribed was high due to the group home environment and is a strength.

The ability to recruit those on typical antipsychotics was hindered by the changeover to a new generation of antipsychotic medications at the study’s site. At the time of the study, approximately 20% of patients were prescribed typical antipsychotics; 30% were on a combination of typical and atypical antipsychotics, and 50% were on atypical antipsychotics. This dispersion is reflected in the recruited subjects with 30 of the 49 being on atypical antipsychotic medications. Those with higher AIMS scores were those who had been changed to atypical medications at least two years earlier, and tardive
dyskinesia with long-term typical antipsychotics in the past are not curable (Sachdev, 2000).

None of the participants refused blood draws for nicotine and cotinine analysis. This is in contrast to the studies of Evins, et al. (2001) and George et al. (2002) who experienced significant refusals resulting in their analyses of data subsets. The ability to obtain blood specimens at all visits was enhanced by use of an intravenous saline lok which may have been more acceptable to the subjects compared to venipuncture technique. The use of the CReSS portable hand-held topography device in this population is still relatively new. The current study results support findings of Tidey et al. (2005) of good test-retest reliabilities in their study reflective of 16 subjects with schizophrenia and their smoking patterns with two topography assessments. Since the results of the current study were similar to those in the Tidey et al. study, the validity of the measures as typical smoking behavior in this population is strengthened.

Topography and Smoke Constituent Exposure at Baseline

The participants (n=49) in the current study overwhelmingly (over 90%) smoked generic, filtered, non-menthol, high tar and nicotine cigarettes. This is higher than the 50% who smoked high tar cigarettes reported in the findings of O’Farrell and colleagues (1983). At baseline, these participants had several markers indicative of greater nicotine dependency than those in Tidey et al. (2005) study with a sample of 20. These included: more average puffs per cigarette (16.3± 8.3 in the current study vs. 12.3± 6.0 in Tidey study), shorter average interpuff interval (15.3± 9.8 seconds in the current study vs. 21.9± 9.7 seconds in Tidey study), slightly longer mean puff duration (1.3±0.4 seconds in the
current study vs. 1.1± 0.4 seconds in Tidey study), and considerably higher mean CO boost per cigarette (6.7± 4.3 in the current study vs. 0.8± 1.5 in Tidey study). The CO boost in the current study was calculated by subtracting the pre-cigarette CO level from post-cigarette level after smoking one cigarette. The study of Tidey and associates calculated CO boost per cigarette by dividing the 90-minute *ad libitum* smoking session CO boost by the number of cigarettes smoked in that timeframe. Participants in the current study on TYP antipsychotics had similar findings to those in Tidey et al. study (2005) of 20 subjects with 7 on TYP antipsychotics, 10 on ATYP antipsychotics, and 3 on no medication. Persons in both studies on TYP antipsychotics smoked more cigarettes a day, had higher FTND scores and greater CO boost per cigarette than those on ATYP medications; these differences were significant in the Tidey et al. study, but nonsignificant in the current study. Both studies found that those on TYP medications had nonsignificantly lower puff volume, nonsignificantly more puffs per cigarette, and nonsignificantly lower peak flow of puff than those on ATYP antipsychotics.

*Topography and Smoke Constituent Exposure Over Eight-week Study*

The findings of the current study support the suggestion of Olincy et al. (1997) that persons with schizophrenia smoke more intensely than other smokers. The topography results of these smokers with schizophrenia were similar to participants in the study by Tidey and colleagues (2005) who found several significant smoking differences between those with schizophrenia and those who did not have a major mental illness. The current study did not find consistent significant differences between those on typical and atypical antipsychotics and their smoke exposure and topography (nicotine boost was lower in
those on TYP antipsychotics with \( p = 0.06 \); interpuff interval was shorter in those on TYP medication with \( p = 0.07 \). Bridges and colleagues (1990) found that shorter interpuff intervals were the strongest contributor to higher blood nicotine levels. The study of Tidey et al. did not include plasma nicotine levels; the current study found that interpuff interval and pre-cigarette nicotine level at visit four was significantly correlated \( r = 0.52, p = 0.01, n = 25 \). In the regression analysis, the interpuff interval did not contribute significantly to the plasma nicotine concentrations at either visit one or visit four. Shorter interpuff intervals contributed to increased post-cigarette CO levels at visit one.

Additional studies on topography and nicotine levels are indicated in this population.

The smoke constituent exposure of those on both TYP and ATYP antipsychotics were affected by treatment of bupropion with nicotine and cotinine post-cigarette significantly lower at the end of eight weeks of therapy \( p = 0.04 \) and \( 0.01 \), respectively. In addition, there were significant \( p = 0.04 \) within group differences with individuals taking atypical antipsychotics decreasing from 44.4 ng/ml post-cigarette nicotine levels at baseline to 34.4 ng/ml at eight weeks, and approached significance for cotinine concentration changes from 294.0 ng/ml to 225.9 ng/ml at eight weeks \( p = 0.07 \). Therefore, bupropion is an effective agent in decreasing the amount of nicotine and cotinine exposure in those with schizophrenia whether on atypical or typical antipsychotics. The differences were not as pronounced with those on typical antipsychotics once again reinforcing that these medications are associated with higher rates of smoking and perhaps are used to treat those with a greater severity of illness.
Strengths of this study included a repeated-measures design with participants as their own control for factors such as metabolism, smoking patterns, and usual brand of cigarette. The four measures helped improve validity. Limitations of the study were the sample size and drop out rate. The study was representative of the predominantly male population in the Veteran population; additional studies are needed in the female veteran population.

*Harm Reduction*

The current study incorporated multiple measures to examine the biobehavioral characteristics of smoking in persons with schizophrenia. High smoking prevalence in persons with schizophrenia places them at increased risk for smoking-related illnesses and diseases. Studies such as this one which show decreasing trends of smoke constituent exposure with interventions such as bupropion provide preliminary information related to potential harm reduction efforts in this population. This study found that the use of bupropion could reduce smoke constituent exposure and affect smoking patterns in individuals who were not interested in cessation nor enrolled in a lengthy smoking cessation program. A long-term reduction in consumption of tobacco may be the second best goal for those who have been unsuccessful at cessation or do not wish to quit smoking. Smoking fewer cigarettes leading to a reduced intake of toxic substances could translate into major health benefits, particularly in those diseases which have shown a tobacco dose dependent risk such as cardiovascular disorders (USDHHS, 1984), pulmonary disorders (USDHHS, 1984; Dockery, et al., 1988), cancer (USDHHS, 1990), and problems during pregnancy (Li, Windsor, Perkins, Goldenberg, & Lowe, 1993).
Based on Austrian data, it is estimated that a 1% reduction in smoking prevalence in the Europe Union would save 1,000 lives annually (Jimenez-Ruiz, Kunze, & Fagerstrom, 1998). Since it is difficult to estimate potential health gains in persons who reduce smoking (Jimenez-Ruiz, et al., 1998), more research is needed to answer this question. Efforts must be ongoing by healthcare providers to repeatedly educate and prescribe interventions to reduce effects of high cigarette smoke exposure.

**Future Directions**

In conclusion, this study’s results offer further evidence that cigarette smoking among those with schizophrenia is not an intractable problem. Bupropion in this time-limited study affected smoking patterns in those with schizophrenia. The shorter time of the cigarette being smoked over the study’s eight-weeks along with decreased nicotine and cotinine levels are encouraging as determinants of less nicotine dependence. Relapse to smoking is high; longer duration of bupropion therapy needs to be studied for smoking cessation outcomes as well as harm reduction impact. Smoking reduction and cessation are not unattainable in smokers with schizophrenia. The findings may have clinical application as prescribing bupropion may be useful for smokers with schizophrenia requiring hospitalization in non-smoking inpatient units. Whether longer duration of bupropion therapy or a combination with nicotine replacement therapy or cessation classes could add to efficacy is another empirical question that warrants further investigation.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
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<td>Smoke constituent exposure</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Smoking topography</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>MADRS</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PANSS</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AIMS</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Self-reported data</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Note. Bupropion started at baseline and continued 8 weeks.
FTND = Fagerstrom test for nicotine dependence
MADRS = Montgomery-Asberg depression rating scale
PANSS = Positive and negative symptom scale for schizophrenia
AIMS = Abnormal involuntary movement scale

Table 3.1
Timeline of data collection for each measure
<table>
<thead>
<tr>
<th>Measure</th>
<th>Total (n=49)</th>
<th>Atypical Med (n=30)</th>
<th>Typical med (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50.5± 5.5</td>
<td>50.0±4.9</td>
<td>51.3 ±6.4</td>
</tr>
<tr>
<td>(n=49)</td>
<td>(n=30)</td>
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<td></td>
</tr>
<tr>
<td>Gender-male ( % total &amp; subgroup)</td>
<td>98 (n=48)</td>
<td>98 (n=29)</td>
<td>100 (n=19)</td>
</tr>
<tr>
<td>Race/ethnicity ( % total &amp; subgroup)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>78 (n=36)</td>
<td>47 (n=23)</td>
<td>27 (n=13)</td>
</tr>
<tr>
<td>African-American</td>
<td>22 (n=13)</td>
<td>14 (n=7)</td>
<td>12 (n=6)</td>
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<tr>
<td>Years of education ( % total &amp; subgroup)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>8 years</td>
<td>4 (n=2)</td>
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<td>4 (n=2)</td>
</tr>
<tr>
<td>9-11 years</td>
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<td>12 (n=6)</td>
<td>2 (n=1)</td>
</tr>
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<td>12 years or GED</td>
<td>61 (n=30)</td>
<td>33 (n=17)</td>
<td>29 (n=13)</td>
</tr>
<tr>
<td>1-3 years college</td>
<td>21 (n=10)</td>
<td>14 (n=7)</td>
<td>6 (n=3)</td>
</tr>
<tr>
<td>Employed full or part time</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Self report cigarettes smoked per day</td>
<td>22.4±12.5</td>
<td>20.3±10.5</td>
<td>25.7±14.9</td>
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<tr>
<td>FTND score</td>
<td>5.3±2.5</td>
<td>5.1 ±2.3</td>
<td>5.6 ±2.9</td>
</tr>
<tr>
<td>PANSS positive scale score</td>
<td>14.2±6.0</td>
<td>15.1 ±6.2</td>
<td>12.8 ±5.4</td>
</tr>
<tr>
<td>PANSS negative scale score</td>
<td>15.0±5.7</td>
<td>15.2 ±5.3</td>
<td>14.7 ±6.3</td>
</tr>
<tr>
<td>PANSS general scale score</td>
<td>29.7±10.2</td>
<td>31.8 ±17.2</td>
<td>28.4 ±8.4</td>
</tr>
<tr>
<td>MADRS scale score</td>
<td>7.2±7.0</td>
<td>7.9 ±6.9</td>
<td>6.0±7.1</td>
</tr>
<tr>
<td>AIMS orofacial scale score</td>
<td>.2±.6</td>
<td>.2 ±.7</td>
<td>.1 ±.2</td>
</tr>
<tr>
<td>AIMS extremity scale score</td>
<td>.1±.3</td>
<td>.1 ±.3</td>
<td>.1 ±.3</td>
</tr>
<tr>
<td>AIMS global judgment scale score</td>
<td>.5±1.2</td>
<td>.6±1.4</td>
<td>.3±.8</td>
</tr>
<tr>
<td>Weight (pounds)</td>
<td>193.6±37.7</td>
<td>198.8±40.6</td>
<td>185.5±31.9</td>
</tr>
</tbody>
</table>

Note. Nonparametric tests used for AIMS
FTND = Fagerstrom test for nicotine dependence
PANSS = Positive and negative symptom scale for schizophrenia
MADRS = Montgomery-Asberg depression rating scale
AIMS = Abnormal involuntary movement scale

Table 3.2
Demographic and baseline smoking characteristics of total sample and by atypical or typical antipsychotic medication category
<table>
<thead>
<tr>
<th>Measure</th>
<th>Total (n=49)</th>
<th>ATYP (n=30)</th>
<th>TYP (n=19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO pre smoking (ppm)</td>
<td>18.5±10.1</td>
<td>17.5 ±8.6</td>
<td>20.1 ±12.2</td>
<td>.15</td>
</tr>
<tr>
<td>CO post smoking (ppm)</td>
<td>25.2±11.1</td>
<td>23.9 ±10.2</td>
<td>27.4 ±12.3</td>
<td>.27</td>
</tr>
<tr>
<td>CO boost (ppm)</td>
<td>6.7±4.3</td>
<td>6.4 ±4.6</td>
<td>7.3 ±4.0</td>
<td>.60</td>
</tr>
<tr>
<td>Nicotine pre-smoking (ng/ml)</td>
<td>17.3±12.7 (n=48)</td>
<td>17.7 ±13.2 (n=48)</td>
<td>16.8 ±12.0 (n=18)</td>
<td>.91</td>
</tr>
<tr>
<td>Nicotine post-smoking (ng/ml)</td>
<td>37.0±19.1 (n=48)</td>
<td>41.5 ±19.1 (n=48)</td>
<td>29.4 ±17.1 (n=18)</td>
<td>.51</td>
</tr>
<tr>
<td>Nicotine boost (ng/ml)</td>
<td>19.6±14.1 (n=48)</td>
<td>23.9 ±14.4 (n=48)</td>
<td>12.6 ±10.6 (n=18)</td>
<td>.06</td>
</tr>
<tr>
<td>Cotinine pre-smoking (ng/ml)</td>
<td>259.8±164.3 (n=48)</td>
<td>265.8 ±175.7 (n=48)</td>
<td>251.1 ±147.7 (n=18)</td>
<td>.76</td>
</tr>
<tr>
<td>Cotinine post-smoking (ng/ml)</td>
<td>276.4±155.1 (n=48)</td>
<td>279.9 ±162.4 (n=48)</td>
<td>270.5 ±146.5 (n=18)</td>
<td>.95</td>
</tr>
<tr>
<td>Butt length after smoking 1 cigarette (mm)</td>
<td>16±10</td>
<td>16 ±11</td>
<td>17 ±9</td>
<td>.27</td>
</tr>
<tr>
<td>Puffs per cigarette</td>
<td>16.3±8.3</td>
<td>15.7 ±7.3</td>
<td>17.4±9.8</td>
<td>.11</td>
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<tr>
<td>Puff volume (ml)</td>
<td>42.1±18.0</td>
<td>42.8 ±19.4</td>
<td>41.0 ±16.1</td>
<td>.74</td>
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<tr>
<td>Average flow per puff (ml/sec)</td>
<td>33.9±9.3</td>
<td>34.5 ±9.3</td>
<td>32.9 ±9.4</td>
<td>.56</td>
</tr>
<tr>
<td>Peak flow of puff (ml/sec)</td>
<td>47.1±15.0</td>
<td>47.9 ±15.2</td>
<td>45.8 ±14.9</td>
<td>.64</td>
</tr>
<tr>
<td>Duration of puff (sec)</td>
<td>1.3±.4</td>
<td>1.3 ±.5</td>
<td>1.3 ±.4</td>
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<tr>
<td>Interpuff interval (sec)</td>
<td>15.3±9.8</td>
<td>17.3 ±10.7</td>
<td>12.2 ±7.3</td>
<td>.07</td>
</tr>
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Table 3.3
Biological and smoking topography measures at baseline total sample and participants on atypical (ATYP) and typical (TYP) medications
<table>
<thead>
<tr>
<th>Measure</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ATYP (n=30)</td>
<td>ATYP (n=20)</td>
<td>ATYP (n=19)</td>
<td>ATYP (n=16)</td>
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<td>TYP (n=11)</td>
<td>TYP (n=10)</td>
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<tr>
<td>Mean puff volume (ml)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATYP</td>
<td>42.8 ± 19.4</td>
<td>39.1 ± 12.9</td>
<td>37.9 ± 13.8</td>
<td>40.5 ± 16.5</td>
</tr>
<tr>
<td>TYP</td>
<td>41.0 ± 16.1</td>
<td>44.2 ± 21.3</td>
<td>40.9 ± 18.4</td>
<td>46.3 ± 22.7</td>
</tr>
<tr>
<td>Mean flow (ml/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATYP</td>
<td>34.5 ± 9.3</td>
<td>32.5 ± 10.6</td>
<td>33.2 ± 10.6</td>
<td>35.1 ± 11.2</td>
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<tr>
<td>TYP</td>
<td>32.9 ± 9.4</td>
<td>34.8 ± 11.9</td>
<td>32.0 ± 9.9</td>
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<td>Peak flow (ml/sec)</td>
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<tr>
<td>ATYP</td>
<td>47.9 ± 15.2</td>
<td>46.7 ± 19.8</td>
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<tr>
<td>TYP</td>
<td>45.8 ± 14.9</td>
<td>49.0 ± 17.6</td>
<td>44.6 ± 15.1</td>
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<td>Interpuff interval (sec)</td>
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<tr>
<td>ATYP</td>
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<td>14.1 ± 12.6</td>
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<td>16.7 ± 14.6</td>
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<td>TYP</td>
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<td>Mean time of peak flow (sec)</td>
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<tr>
<td>ATYP</td>
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<td>.3 ± .1</td>
<td>.3 ± .1</td>
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<tr>
<td>TYP</td>
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<td>.3 ± .2</td>
<td>.3 ± .1</td>
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<tr>
<td>Puffs per cigarette</td>
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<td></td>
</tr>
<tr>
<td>ATYP</td>
<td>15.6 ± 7.3</td>
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<td>TYP</td>
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<td>15.9 ± 7.7</td>
<td>18.3 ± 6.7</td>
<td>14.6±7.0</td>
</tr>
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<td>CO boost (ppm)</td>
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</tr>
<tr>
<td>ATYP</td>
<td>6.4±4.6</td>
<td>4.6±2.9</td>
<td>5.1±3.6</td>
<td>5.3±3.3</td>
</tr>
<tr>
<td>TYP</td>
<td>7.3±3.9</td>
<td>9.3±7.9</td>
<td>6.9±4.3</td>
<td>7.6±5.3</td>
</tr>
</tbody>
</table>

Table 3.4
Smoking topography measures for participants on atypical (ATYP) and typical (TYP) medications at visits 1 through 4 (n ranges from 25 to 49)
<table>
<thead>
<tr>
<th>Measure</th>
<th>Visit 1 (n=48)</th>
<th>Visit 4 (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine pre-cigarette (ng/ml)</td>
<td>17.3±12.7</td>
<td>15.9±10.0</td>
</tr>
<tr>
<td>Nicotine post-cigarette (ng/ml)</td>
<td>37.0±19.1</td>
<td>33.5±14.9</td>
</tr>
<tr>
<td>Nicotine boost (ng/ml)</td>
<td>19.6±14.1</td>
<td>17.6±15.8</td>
</tr>
<tr>
<td>Cotinine pre-cigarette (ng/ml)</td>
<td>259.8±164.3</td>
<td>256.8±161.1</td>
</tr>
<tr>
<td>Cotinine post-cigarette (ng/ml)</td>
<td>276.4±155.1</td>
<td>253.7±160.7</td>
</tr>
</tbody>
</table>

Table 3.5  
Nicotine and cotinine measures at visit 1 and visit 4
<table>
<thead>
<tr>
<th>Measure</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Significance of Within subject effects</th>
<th>Significance of Between subject effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean puff volume (ml) ATYP</td>
<td>38.0 ± 17.7</td>
<td>37.9 ± 12.6</td>
<td>38.6 ± 14.6</td>
<td>40.5 ± 16.5</td>
<td>.42</td>
<td>.48</td>
</tr>
<tr>
<td>Mean puff volume (ml) TYP</td>
<td>41.9 ± 17.8</td>
<td>45.3 ± 23.4</td>
<td>40.6 ± 19.5</td>
<td>46.3 ± 22.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean flow (ml/sec) ATYP</td>
<td>31.3 ± 8.6</td>
<td>31.2 ± 9.7</td>
<td>32.4 ± 10.3</td>
<td>35.1 ± 11.2</td>
<td>.01</td>
<td>.98</td>
</tr>
<tr>
<td>Mean flow (ml/sec) TYP</td>
<td>30.9 ± 10.1</td>
<td>34.4 ± 13.1</td>
<td>31.0 ± 9.9</td>
<td>34.2 ± 11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean peak flow (ml/sec) ATYP</td>
<td>42.2 ± 12.9</td>
<td>44.2 ± 18.0</td>
<td>46.0 ± 17.7</td>
<td>49.7 ± 18.0</td>
<td>.01</td>
<td>.88</td>
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<tr>
<td>Mean peak flow (ml/sec) TYP</td>
<td>40.9 ± 15.3</td>
<td>47.2 ± 19.0</td>
<td>42.4 ± 14.2</td>
<td>47.7 ± 17.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interpuff interval (sec) ATYP</td>
<td>17.2 ± 12.4</td>
<td>15.3 ± 13.9</td>
<td>13.9 ± 9.9</td>
<td>16.7 ± 14.6</td>
<td>.03</td>
<td>.72</td>
</tr>
<tr>
<td>Interpuff interval (sec) TYP</td>
<td>14.6 ± 8.8</td>
<td>15.3 ± 13.3</td>
<td>10.2 ± 4.6</td>
<td>16.2 ± 11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time of peak flow (ms) ATYP</td>
<td>331.1 ± 131.5</td>
<td>328.7 ± 137.5</td>
<td>294.9 ± 110.6</td>
<td>273.9 ± 69.0</td>
<td>.64</td>
<td>.44</td>
</tr>
<tr>
<td>Mean time of peak flow (ms) TYP</td>
<td>331.2 ± 122.0</td>
<td>308.6 ± 162.2</td>
<td>322.2 ± 163.9</td>
<td>280.2 ± 118.0</td>
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<tr>
<td>Puffs per cigarette ATYP</td>
<td>15.6 ± 7.3</td>
<td>18.6 ± 5.9</td>
<td>18.1 ± 8.4</td>
<td>14.0 ± 6.5</td>
<td>.59</td>
<td>.61</td>
</tr>
<tr>
<td>Puffs per cigarette TYP</td>
<td>17.4 ± 9.8</td>
<td>15.9 ± 7.7</td>
<td>18.3 ± 6.7</td>
<td>14.6 ± 7.0</td>
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<tr>
<td>Duration of puffs ATYP</td>
<td>1.3±.5</td>
<td>1.3±.4</td>
<td>1.3±.5</td>
<td>1.2±.4</td>
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<td>.59</td>
</tr>
<tr>
<td>Duration of puffs TYP</td>
<td>1.4±3</td>
<td>1.3±3</td>
<td>1.3±3</td>
<td>1.4±4</td>
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<tr>
<td>CO boost ATYP</td>
<td>7.2±5.4</td>
<td>4.9±3.0</td>
<td>5.6±3.4</td>
<td>5.3±3.3</td>
<td>.43</td>
<td>.03</td>
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<tr>
<td>CO boost TYP</td>
<td>8.0±4.8</td>
<td>11.0±8.5</td>
<td>6.6±4.4</td>
<td>7.6±5.3</td>
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</table>

Table 3.6
Smoking topography measures for participants on atypical (ATYP) and typical (TYP) medications completing all four visits (total n=25; ATYP=16; TYP=9)
Table 3.6 continued

<table>
<thead>
<tr>
<th>Measure</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Significance of Within subject effects</th>
<th>Significance of Between subject effects</th>
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<tbody>
<tr>
<td>Time to smoke one cigarette (min)</td>
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<td>ATYP</td>
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<td>TYP</td>
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<tr>
<td>Butt length (mm)</td>
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<tr>
<td>ATYP</td>
<td>18±13</td>
<td>17±12</td>
<td>19±17</td>
<td>22±15</td>
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<td>.31</td>
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<tr>
<td>TYP</td>
<td>19±7</td>
<td>24±14</td>
<td>16±13</td>
<td>18±14</td>
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<tr>
<td>Weight (pounds)</td>
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</tr>
<tr>
<td>ATYP</td>
<td>195.0±40.6</td>
<td>192.9±39.0</td>
<td>195.2±40.0</td>
<td>195.1±40.4</td>
<td>.71</td>
<td>.26</td>
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<tr>
<td>TYP</td>
<td>178.2±23.1</td>
<td>178.6±22.7</td>
<td>177.9±22.7</td>
<td>176.4±20.9</td>
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</tr>
<tr>
<td>ATYP</td>
<td>4.5±2.1</td>
<td>4.3±2.3</td>
<td>4.±2.6</td>
<td>3.5±2.2</td>
<td>.27</td>
<td>.26</td>
</tr>
<tr>
<td>TYP</td>
<td>5.3±3.2</td>
<td>5.8±3.4</td>
<td>4.8±3.4</td>
<td>5.3±3.0</td>
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</tr>
<tr>
<td>Reported number of cigarettes smoked per day</td>
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</tr>
<tr>
<td>ATYP</td>
<td>19.4±11.1</td>
<td>17.9±10.5</td>
<td>16.4±13.1</td>
<td>16.7±8.5</td>
<td>.29</td>
<td>.08</td>
</tr>
<tr>
<td>TYP</td>
<td>28.0±19.5</td>
<td>26.0±19.5</td>
<td>29.2±21.2</td>
<td>20.4±8.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measure</td>
<td>Visit 1</td>
<td>Visit 4</td>
<td>Within subjects effects</td>
<td>Between subjects effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-------------------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine pre-cigarette</td>
<td>ATYP</td>
<td>19.1±15.4</td>
<td>14.0±8.8</td>
<td>.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TYP</td>
<td>22.2±11.3</td>
<td>19.2±11.9</td>
<td>.74</td>
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<tr>
<td>Nicotine post-cigarette</td>
<td>ATYP</td>
<td>44.4±16.4</td>
<td>34.4±16.5</td>
<td>.04</td>
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</tr>
<tr>
<td></td>
<td>TYP</td>
<td>35.7±15.6</td>
<td>31.9±12.3</td>
<td>.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine boost</td>
<td>ATYP</td>
<td>19.4±2.6</td>
<td>20.3±18.4</td>
<td>.49</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>TYP</td>
<td>16.5±3.3</td>
<td>12.7±8.5</td>
<td>.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotinine pre-cigarette</td>
<td>ATYP</td>
<td>276.4±176.1</td>
<td>235.0±159.2</td>
<td>.37</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>TYP</td>
<td>308.2±127.8</td>
<td>295.4±166.4</td>
<td>.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotinine post-cigarette</td>
<td>ATYP</td>
<td>294.9±160.5</td>
<td>225.9±157.3</td>
<td>.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TYP</td>
<td>335.4±129.3</td>
<td>303.0±163.7</td>
<td>.33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Atypical (n=16); Typical (9)

Table 3.7
Biological markers for participants on atypical (ATYP) and typical (TYP) medications at visit 1 and visit 4
<table>
<thead>
<tr>
<th>Measure</th>
<th>Z value (based on positive ranks)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine pre-cigarette</td>
<td>-1.34</td>
<td>.18</td>
</tr>
<tr>
<td>Nicotine post-cigarette</td>
<td>-2.03</td>
<td>.04</td>
</tr>
<tr>
<td>Nicotine boost</td>
<td>-1.20</td>
<td>.23</td>
</tr>
<tr>
<td>Cotinine pre-cigarette</td>
<td>-1.08</td>
<td>.28</td>
</tr>
<tr>
<td>Cotinine post-cigarette</td>
<td>-2.52</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Asymp. Sig (2-tailed)

Table 3.8
Paired samples Wilcoxon test for participants completing all four visits by ATYP and TYP antipsychotic medication category (n=25)
Figure 3.1 Significant within group changes using paired samples Wilcoxon test for post nicotine in ng/ml (n=25)
Figure 3.2 Significant within group changes using paired samples Wilcoxon test for post cotinine in ng/ml (n=25)


Yerardi, R.S. & Ahijevych, K. (2007). *Special considerations in conducting research with persons who have schizophrenia. Manuscript submitted for publication.*


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