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Anne Reynolds April 10th, 2016

Nicotine Usage in Individuals at Clinical High Risk of Developing Psychosis

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Abstract

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Substance abuse is common among individuals with a psychotic disorder. The rate of nicotine use in psychotic populations is estimated around 75% or higher. One explanation for this elevated smoking rate is the self-medication hypothesis, in which psychotic individuals use nicotine to alleviate aspects of psychosis such as cognitive deficits and negative symptoms. These benefits are postulated to be related to nicotine's role in dopamine production in the brain. Evidence is mixed, with some studies finding cognitive benefits associated with nicotine, some finding an association between nicotine and negative symptom severity, and some finding no relationship. Little research examines this theory in individuals at Clinical-High Risk (CHR) of developing psychosis. The current study investigated the relationship between negative symptom severity in a sample of CHR individuals taken from the NAPLS 2 study and hypothesized that smoking rates would be elevated among this population compared to healthy controls and that there would be a positive association between symptom severity at the baseline and 12 month visits. Additionally, the current study hypothesized that nicotine users would have a decrease in symptom severity over time. CHR individuals exhibited an elevated smoking rate. Findings did not support the self-medication hypothesis, as a positive relationship was observed in only two symptoms at baseline and none at 12 months and no relationship was found between baseline nicotine use and symptom severity over time. No relationship was found between nicotine and mean negative symptom score. An inverse relationship found between social anhedonia and nicotine use at both time-points may indicate the opposite – that symptom severity discourages smoking behaviors. This is further explained by past research findings indicating that youth with higher levels of social connectedness are more likely to use nicotine later in life.

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Nicotine Usage in Individuals at Clinical High Risk of Developing Psychosis

Substance abuse is a common problem among individuals diagnosed with a psychotic illness (Kerner, 2014). The illicit substance most commonly abused by these individuals is cannabis, the use of which has been increasingly implicated as a risk factor for the development of a psychotic illness (Bersani, Orlandi, Kotzalidis, & Pancheri, 2002). However, psychotic populations appear to use a number of other substances at a rate significantly higher than that found in the general population – in particular, these individuals exhibit high levels of nicotine usage (Dalack et al., 1998). Nicotine is a highly addictive substance most commonly ingested through the smoking of cigarettes, although alternative methods (e.g., chewing gum and patches) are available. Individuals diagnosed with a psychotic disorder appear to be particularly dependent on cigarettes, exhibiting a within-population proportion of smokers exceeding 75%, as compared to the proportion of smokers in the general population, which has fallen below 25% (Berg et al., 2013). The proportion of psychotic patients who are smokers also significantly exceeds the proportion found in samples diagnosed with other psychiatric illnesses (Dalack et al., 1998). In addition, individuals diagnosed with a psychotic disorder are less likely to quit smoking cigarettes, despite the widely-known carcinogenic risks associated with the toxic chemicals inhaled in cigarette smoke (Tidey, Colby, & Xavier, 2013).

The precise reasons for the hyper-elevated smoking rate present in psychotic populations are unclear; however, several explanations for this dependent behavior utilize a "self-medication" theory regarding the potential therapeutic role of nicotine in relieving symptoms or medication side effects associated with psychotic illness (Kumari & Postma, 2005). One version of this theory postulates that individuals with a psychotic disorder smoke in order to alleviate several of the symptoms associated with their illness (Kumari & Postma, 2005). In particular, it

appears that nicotine may be effective in addressing several of the cognitive deficits associated with psychotic illness, such as problems with working memory and attention (Kumari & Postma, 2005). In addition, it is also possible that nicotine may be related to a reduction in psychiatric symptoms, particularly the negative symptoms (e.g., social anhedonia, avolition) of schizophrenia, and/or to relieve the noxious side effects related to the use of antipsychotics needed to treat the symptoms of the disorder (Aguilar, Gurpegui, Diaz, & de Leon, 2005).

Statement of Goals

Although the relationship between nicotine usage and psychotic illness has been well established, there are no universally agreed upon explanations regarding the causal nature of the relationship between the use of this particular substance and its role in mental health. In addition, very little research has been conducted on the role of nicotine in use in the prodromal phase of psychosis. This prodromal phase is the period of functional decline and increasing symptom severity that precedes the onset of psychosis and can be a few months or several years in duration (Goulding et al., 2013). These individuals, deemed at "Clinical-High Risk" (CHR) of developing psychosis, often experience attenuated versions of the symptoms typical of a psychotic disorder, such as hallucinations and paranoia, but at a level of conviction and severity below that required for the diagnosis of a psychotic disorder (Goulding et al, 2013). Because CHR individuals are typically not medicated, this group provides the opportunity to study the relation of pre-psychotic symptoms with smoking in the absence of the confound presented by the use of psychotropic medication. Further, longitudinal studies of the relation between baseline smoking and current and follow-up symptom severity offer a firmer basis for drawing inferences about causal mechanisms. Thus, while ethical guidelines preclude experimental studies of the effects of smoking on patient symptoms, in that nonsmokers cannot be asked to

smoke for experimental purposes, longitudinal studies can shed light on relationships that may have causal implications.

The primary goal of this study is to examine the smoking behaviors of a group of CHR individuals in order to determine whether the elevated smoking rate typically observed in psychotic populations is evident in individuals who have not yet transitioned to a more serious mental illness. In addition, this study will also aim to examine the relationship between smoking behavior in CHR individuals as it relates to symptom presentation and course in order to ascertain whether there is a relationship that offers insight into the determinants of nicotine use in this population and the role that nicotine may play in the symptom presentation. By doing so, this study will help to further knowledge of the prodromal period and in particular the factors underlying such high rates of nicotine use by psychotic patients. Indeed, this link is an important one to study – the extensive use of cigarettes by psychotic patients contributes to elevated rates of unnatural causes of death, led by cardiovascular complications that can be directly linked to the toxic influence of chemicals contained in cigarette smoke (Brown et al., 2013). Further knowledge regarding the correlates of nicotine use in afflicted individuals is thus an important goal to pursue.

The Neurobiological Role of Nicotine

Nicotine appears to exert most of its influence on users through its effects on the production of dopamine in the brain (Lyon, 1999). The use of nicotine has been shown to stimulate mesolimbocorticol dopaminergic activity in areas of the brain that have been linked to some of the symptoms of psychotic illness (Lyon, 1999). This mesolimbocorticol dopaminergic system, which extends from the ventral tegmental area of the brain to the nucleus accumbens, the medial prefrontal cortex, and the central nucleus of the amygdala, plays a key role in the

formation of dependence to nicotine (Nomikos et al., 2000). Studies performed using rats as experimental subjects support this, noting an increase in the self-administration of nicotine in test subjects when neurons in the mesolimbocorticol pathway are lesioned (Nomikos et al., 2000). In addition, extensive exposure to nicotine, such as that found in individuals highly dependent upon cigarettes, can result in the desensitization of receptors found in the mesolimbocorticol pathways, which can subsequently explain the formation of tolerance to nicotine's effects on the production of dopamine (and thus the pleasurable effects felt from the consumption of the chemical) (Benwell, Balfour, & Birrell, 1995).

Nicotine interacts with a number of different neurotransmitter receptors in the brain, but there are specific receptors that are important in explaining nicotine's role in the brain as it pertains to symptoms of psychotic illness (Domino, Mirzoyan, & Tsukada, 2004). One such receptor implicated in having such a role is the $\alpha 7$ nicotinic acetylcholine receptor, which is present in significantly fewer numbers (particularly in the hippocampus) in individuals with a psychotic illness (Marutle et al., 2001). Psychotic individuals also appear to have decreased numbers of high-affinity nicotinic receptors, which are typically observed in healthy individuals with a smoking habit (Leonard et al., 2000). In fact, the locus of the gene on chromosome 15 associated with $\alpha 7$ nicotinic receptors has been linked to a particular psychophysiological deficit found in schizophrenic individuals known as the P50 auditory sensory deficit, indicating a close relationship between this particular type of receptor and the biological underpinnings of at least one symptom of psychotic illness (Nomikos et al., 2000). However, nicotine use by individuals in which this P50 deficit is observed appears to be instrumental in correcting for the problem, further establishing the link between this particular nicotinic receptor and psychotic illness (Leonard et al, 2000). It is also possible that $\alpha 7$ nicotinic receptors are indirectly responsible for

the effects of nicotine by encouraging the release of glutamate, which has a stimulating effect on dopamine-producing neurons located in mesolimbocorticol pathway (Di Chiara, 2000). Polymorphisms of the α7 nicotinic receptor have been linked with an increased likelihood of developing a dependence on nicotine – indeed, Brunzell and McIntosh (2011) found that antagonizing select α7 nicotinic receptors in rats encouraged the pursuit of the consumption of nicotine.

The Rate and Predictors of Smoking in Psychotic and CHR Individuals

Smoking behavior in CHR and psychotic individuals can be influenced by a number of different factors. It is clear that the rate of smoking in psychotic populations is extremely high – as previously stated, this rate is typically cited as being 70-75% or higher within this population as opposed to a much lower smoking rate in the general population (Berg et al., 2013). Smoking rates within CHR populations have not been as well documented; however, a study conducted by Gupta and Mittal in 2014 found a smoking rate of 46% within their CHR group as opposed to 22% within their group of healthy control participants. Addington et al. (2014) conducted a literature review of documented substance abuse in CHR individuals and found that nicotine was the third most commonly abused substance in this group (behind cannabis and alcohol), citing a rate of lifetime use in reviewed studies ranging from 16-34%. It is possible that elevated smoking rates are typical of CHR populations similar to the way in which these rates are typical of psychotic populations, although more research on smoking behaviors within CHR populations would have to be conducted in order to establish this (Gupta & Mittal, 2014).

A number of different sociodemographic factors have been found to show some relationship to smoking behaviors in the general population. Age, gender, ethnicity, employment status, and income have all been shown to have an association with the onset and continuation of

smoking behaviors (Thompson, Tebes, & McKee, 2015). Barbeau, Krieger, and Soobader found that low levels of education, working class jobs, and low income were related to higher levels smoking in a 2004 study that utilized data collected in the 2000 National Health Interview Study. Johnson and Novak reported similar findings in a 2009 study conducted using a different data set collected from the National Epidemiologic Study of Alcohol and Related Conditions. In addition, Johnson and Novak (2009) found that men had a slightly higher risk of daily smoking early onset than women. Women do appear to smoke fewer cigarettes per day than men; however, women also find it much harder to quit smoking than their male counterparts (Thompson et al., 2015). In addition, prenatal exposure to nicotine may also be related to an increased risk for smoking later in an individual's life (Cornelius, Leech, Goldschmidt, & Day, 2005).

It is unclear whether factors that are associated with an increased risk of smoking in the general population are similarly associated with risk of smoking in CHR and psychotic individuals, as the extremely high rate of smoking in psychotic populations suggests that there are a number of additional variables influencing the onset of smoking in these individuals (Smith et al., 2009). Smith and colleagues conducted a study on first episode psychosis patients in 2009 in order to address this question and found that low socioeconomic status and prenatal exposure to nicotine were significantly associated with the initiation of smoking behavior in the observed population. These are risk factors that are also significantly associated with the initiation of smoking in the general population, suggesting that some risk factors universally affect both healthy individuals and those that have or will later develop a psychotic disorder (Smith et al., 2009).

It does appear as if there are a number of risk factors that are uniquely related to the number of cigarettes smoked by individuals with a psychotic disorder (Meszaros et al., 2011).

Meszaros et al. (2011) identified the use of typical antipsychotics and treatment-resistant psychosis as being significantly related to the severity of smoking seen in the participants in their study. The relationship between typical antipsychotics and smoking severity is likely due to the effects that such antipsychotics have on dopamine receptors in the brain (de Haan, Booij, & Lavalaye, 2006). These typical antipsychotics (or first-generation antipsychotics) partially block nicotinic receptors in the brain, resulting in lower stimulation of this particular type of receptor by natural means – the resulting deficit of dopamine in the brain encourages the use of nicotine, which stimulates the release of dopamine in the brain and thus increases the chances of dependence on the chemical (Matthews, Wilson, & Mitchell, 2011). In contrast, it is possible that atypical second-generation antipsychotics, such as clozapine, may help reduce smoking in psychotic patients as they affect different chemical receptors (such as serotonin receptors) in the brain (Matthews et al., 2011).

Finally, it is important to note that the abuse of multiple substances simultaneously is an extremely common problem for many individuals with a psychotic illness (Margolese, Malchy, Negrete, Tempier, & Gill, 2004). Cannabis, alcohol, nicotine, and cocaine appear to be the most-abused substances within psychotic populations, and it is likely that a large number of these individuals are dependent on or are at least users of more than one of these substances (Margolese et al., 2004). The use of alcohol and nicotine appear to be related to each other in the general population, so it is possible that this relationship is also present in psychotic populations that use both alcohol and nicotine at much higher rates than typically healthy individuals (Meszaros et al., 2011). Margolese et al. (2004) note that individuals with dual diagnoses of psychosis and a substance abuse disorder were more likely to smoke cigarettes (88.9%) than those with only one diagnosis (49.6%).

The Symptoms Correlates of Smoking in Psychotic Populations

Many studies cite the self-medication hypothesis of substance abuse as a potential explanation for the extremely high levels of nicotine use within psychotic populations (Kumari & Postma, 2005). This theory generally postulates that psychotic individuals display elevated smoking rates because the nicotine contained in cigarettes can help to alleviate several of the deficits and symptoms associated with psychotic illness (Kumari & Postma, 2005). Nicotine has, in some cases, been shown to have a beneficial effect on specific deficits associated with psychotic illness – for example, it has been found that nicotine, through its interactions with the $\alpha 7$ nicotinic receptor, can normalize the auditory gating deficits common in the majority of schizophrenic patients (Nomikos et al., 2000). However, nicotine has also been hypothesized to affect a much larger range of symptoms, which include the cognitive deficits, negative symptoms, and noxious side effects of antipsychotics typically experienced by individuals with a psychotic disorder (Kumari & Postma, 2005). The extent to which nicotine consumption is related to each of these deficits and symptoms is unclear; however, several aspects of this theory have been given credence in recent literature, suggesting that a self-medicating theory of nicotine use could be a valid explanation for smoking behaviors in psychotic populations.

Nicotine and Cognitive Deficits in Psychotic Illness

One key aspect of the self-medication hypothesis postulates that nicotine use can help alleviate several of the cognitive deficits commonly found in psychotic illness (Harris et al., 2004). Cognitive deficits in areas of working memory, attention, executive functioning, and verbal learning are both common in and characteristic of schizophrenia and tend to play an integral role in determining the functional outcome of the afflicted individual (Sharma & Antonova, 2003). It is believed that nicotine, through normalizing effects on cholinergic

receptors in the brain, can have a therapeutic role in treating several of these symptoms.(D'Souza & Markou, 2012). The beneficial effects of nicotine on cognition have been demonstrated in several human subjects studies - Swan and Lessov-Schlagger (2007) note that improved functioning in areas of recognition memory, working memory, and attention has been documented in relation to the use of nicotine in various studies. Unsurprisingly, the brain areas typically associated with these cognitive functions also have large numbers of nicotinic receptors (Kumari & Postma, 2005).

It appears that nicotine can similarly improve cognitive functioning in schizophrenic patients as well. Hong et al. (2011) found that schizophrenic patients demonstrated improvements in sustained attention in response to the application of a dermal nicotine patch. Smith, Singh, Infante, Khandat, and Kloos (2002) noted improved spatial organizational skills in schizophrenic patients in response to the use of nicotine nasal spray as well as slight improvements in tasks involving reaction time and verbal memory. These cognitive benefits are also evident in CHR individuals as well as those that have already developed a psychotic disorder – Gupta and Mittal (2014) documented higher levels of functioning in spatial working memory, processing speed, and visual learning in CHR participants that reported higher levels of smoking. Indeed, the cognitive benefits of nicotine have been so well-established that transdermal nicotine patches have been tested for use as a treatment for patients with Alzheimer's disease or other forms of dementia or cognitive impairments (White & Levin, 2004).

However, it should be noted that although nicotine-related improvements in cognitive functioning have been documented in psychotic and CHR individuals, these improvements do not necessarily normalize deficits in cognitive functioning (Hong et al., 2009). In addition, it is

possible that these cognitive benefits are not the main motivator behind increased smoking rates in psychotic and CHR individuals – Hahn et al. (2013) note that schizophrenic participants in their study did not perform at higher cognitive levels based on the amount of nicotine consumed. However, that does not necessarily mean that nicotine is not important for the functioning of these individuals. For instance, AhnAllen, Bidwell, and Tidey (2014) found that significantly lowering the amount of nicotine contained in cigarettes among schizophrenic and healthy smokers was associated with lowered levels of cognitive functioning in both groups, suggesting that (at least for individuals with an established smoking habit) a certain level of nicotine content is important in order to maintain improvements in functioning.

Nicotine and the Side-Effects of Antipsychotics

Another version of the self-medication hypothesis postulates that psychotic patients smoke at a higher rate because nicotine helps to alleviate some of the noxious side-effects that typically accompany a range of antipsychotics many of these individuals take regularly (Kumari & Postma, 2005). The long-term use of first-generation antipsychotics such as haloperidol can lead to the development of tardive dyskinesia, in which the medicated individual experiences abnormal and involuntary movements (Bordia, McIntosh, & Quik, 2011). As previously stated, these first-generation antipsychotics work primarily by blocking dopamine receptors; however, nicotine can stimulate the production of dopamine in the brain, which may in turn help to alleviate side effects caused by antipsychotics that work in this manner (Bordia et al., 2011). Indeed, Bordia et al. (2011) induced symptoms resembling tardive dyskinesia in mice through the administration of haloperidol and found that treating these mice with nicotine helped to alleviate the symptoms induced by the haloperidol treatment. In addition, there are a number of cognitive deficits – such as impairments in spatial memory and attention – that are related to the

use of haloperidol and can be alleviated through the effects of nicotine (Kumari & Postma, 2005).

Nicotine and the Negative Symptoms of Psychosis

The negative symptoms of schizophrenia and other psychotic disorders, which include a range of symptoms encompassing deficits in motivation, emotional expression, and social functioning, are often significant predictors of later functioning in schizophrenic patients and are also much more difficult to treat with current medications than are the positive symptoms (e g., hallucinations, delusions) (Kalin et al., 2015). It is hypothesized that schizophrenic patients smoke, in part, because the nicotine contained in cigarettes helps to alleviate the negative symptoms that they are experiencing (Kumari & Postma, 2005). This therapeutic effect is thought to be related to the way in which nicotine promotes the production of dopamine in certain areas of the brain (Lyon, 1999). As mentioned, nicotine stimulates mesolimbicocorticol dopaminergic activity in the brain, thus promoting the production of dopamine in prefrontal areas of the brain (Lyon, 1999). Negative symptoms are thought to be caused in part by hypofrontality, in which a much lower than normal amount of blood flows through the prefrontal cortex (Weinberger & Berman, 1988). This condition is often found in schizophrenia patients and is accompanied by negative symptoms that appear related in intensity to the severity of the hypofrontality present in the individual (Weinberger & Berman, 1988).

The evidence regarding this particular aspect of the self-medication hypothesis is mixed. It does appear that newer medications that have more efficacy in treating negative symptoms, such as clozapine, also appear to be related to a decrease in smoking in schizophrenic individuals (Lyon, 1999). An association between negative symptom severity and self-reported nicotine use has been observed in several other samples – for example, Patkar et al. (2002) rated their

participants using the Fagerstrom Test for Nicotine Dependence and found that these scores were significantly and positively correlated with negative symptom severity. This relationship has also been tested in a direct experimental manner. Smith et al. (2002) found that the schizophrenic participants in their study reported a decrease in negative symptoms after smoking either highly nicotinized or denicotinized cigarettes, but that the decrease reported after smoking the highly nicotinized cigarettes was much greater than for those individuals smoking the denicotinized cigarettes.

However, there are multiple studies that report results conflicting with those that are supportive of this aspect of the self-medication hypothesis. For example, although Patkar et al. (2002) found a positive association between nicotine use and negative symptoms in their study, they also note that a number of other studies found either no association or a negative association between nicotine and negative symptoms. Deutsch et al. (2013) experimentally tested this relationship by giving subjects a medication that contained an $\alpha 7$ nicotinic receptor agonist, but found that there were no differences between the experimental and control groups (which received a placebo) in terms of negative symptom outcome. Despite these results, however, there are studies with a similar design that have yielded different findings – Freedman et al. (2008) utilized a different $\alpha 7$ nicotinic agonist and found a significant relationship between the use of this agonist and improvement in negative symptoms in the experimental group in their study.

Alternative Explanations for Smoking in Psychosis

The self-medication hypothesis regarding smoking in psychosis targets several different classes of deficits and symptoms that may be alleviated through the use of nicotine and, to date, there appears to be substantial research supporting aspects of this theory (Kumari & Postma, 2005). However, there are alternative explanations for the heightened smoking rate observed in

psychotic individuals that may also prove to be valid. Instead of smoking in order to self-medicate and relieve symptoms of their disorder, psychotic individuals may exhibit higher levels of nicotine dependence simply because they are much more likely to become addicted than a healthy individual because the neurobiology of their mental illness predisposes them to addiction (Berg et al., 2013). Schizophrenic brains have abnormalities of structure and function in the frontal cortex and hippocampus that may heighten chances of addiction through the encouragement of drug-seeking activities and through the enhancement of the reward received from using the drugs (Chambers, Krystall, & Self, 2001). Berg et al. (2013) tested this theory by using ventral hippocampal lesions to induce symptoms in rats that resemble the cognitive and neurobiological symptoms seen in schizophrenia. The researchers found that animals with lesions received the same cognitive benefit as non-experimental animals after nicotine exposure – that is, animals from both groups performed better on a the same timed task (Berg et al., 2013). Furthermore, a significant impairment in cognitive tasks was noted in lesioned rats previously exposed to nicotine but subsequently deprived of the chemical, suggesting that the observed cognitive benefits associated with nicotine for these rats come with the price of potential greater impairment during withdrawal (Berg et al., 2013). In addition, experimental rats did not receive any cognitive benefits from nicotine in the areas of impairment related to the lesions - they did, however, exhibit an increase in nicotine-seeking behaviors and in overall amount of nicotine consumed (Berg et al., 2013).

Purpose and Hypotheses of the Present Study

Despite the wealth of research regarding nicotine use and schizophrenia, there is little research examining smoking behaviors in CHR individuals. The rate of smoking in psychotic patients is extremely high; however, it appears that the majority of these individuals begin

smoking before the onset of their illness (Riala, Hakko, Isohanni, Pouta, & Rasanan, 2004). This suggests that factors present before the individual experiences a first episode of psychosis are influencing the development of a smoking habit. Indeed, Riala et al. (2004) suggested that smoking may be related to the prodromal phase preceding the onset of psychosis, noting that the initiation of regular smoking in their study population was related to conversion to psychosis and tended to precede conversion by an average of 2.3 years. Thus, it is important to investigate nicotine use in CHR individuals as this may lead to new information regarding what drives these individuals to begin smoking.

In addition, as mentioned above, the high levels of cigarette smoking in schizophrenic populations likely account for a large number of preventable deaths – Brown et al. (2010) note that, in their observed sample, a significant number of deaths among schizophrenic individuals occurred due to cardiovascular complications and that among the cohort of smoking individuals in their study, approximately 70% of excess deaths occurred due to smoking-related diseases. Smoking is known to be linked to cardiovascular complications, in addition to a variety of concerns, such as a heightened risk of developing lung cancer (Brown et al., 2010). Thus, it is important to encourage schizophrenic patients to cease smoking – this, however, is a difficult task, as these smokers experience more severe withdrawal and psychiatric symptoms when attempting to quit smoking and simply find this task to be much harder than healthy individuals (Dalack, Becks, Hill, Pomerleau, & Meador-Woodruff, 1999). In addition, if nicotine is truly therapeutic for these individuals, it is perhaps not best to completely cease consumption of the chemical and instead experiment with alternative forms of nicotine consumption (such as through nicotine patches). More research on the reasons driving CHR and psychotic patients to smoke would help to guide efforts to improve the overall health of these individuals and

additionally serve to further overall knowledge regarding the pathology of substance abuse in psychosis.

Thus, the current study will examine the smoking behavior of CHR individuals in order to further elucidate the relation of nicotine use with symptoms. The self-medication hypothesis cannot be tested directly tested in any clinical sample, as experimental manipulation of cigarette/nicotine use would not conform to IRB guidelines concerning participant risk. However, research on CHR samples may be helpful in identifying aspects of the self-medication hypothesis, in that these samples pose fewer challenges with regard to treatment confounds, in that only a subgroup have been exposed to antipsychotic medication. Also, the study sample, which is drawn from the North American Prodrome Longitudinal Study (NAPLS 2), is large and therefore offers power and flexibility in both size (as the NAPLS 2 data set is the largest of its kind) and in its ability to allow for longitudinal investigation of the relationship between CHR symptom presentation and nicotine use. Another advantage of the NAPLS 2 study is the fact that it is well characterized and data were obtained on all major substances of abuse. This is important because of the high rate of comorbidity in substance use; identifying unique relations for a particular substance requires statistical control for use of other abused substance.

The relationship between negative symptoms and nicotine use has not been examined longitudinally in CHR subjects; thus, this association will be a focus of the current project. It is hypothesized that CHR individuals will smoke at a significantly higher rate than healthy control individuals, although the rate will be lower than that typically reported in psychotic populations. In addition, it is hypothesized that the frequency of smoking in CHR individuals at baseline will be positively associated with the severity of negative symptoms at baseline and, likewise, that the frequency of smoking of CHR individuals at the 12-month follow-up visit will be positively

associated with the severity of negative symptoms at this time-point. Finally, based on the self-medication hypothesis, it is predicted that those CHR participants who are nicotine users at baseline with show a decline in negative symptoms over time.

Methods

NAPLS 2 - Overview

The North American Prodrome Longitudinal Study (NAPLS) was initiated with the purpose of collecting a large database on CHR individuals in order to study factors related to the transition to psychosis. It is a multi-site prospective study with sites located at Emory University, University of North Carolina – Chapel Hill, Yale University, Harvard University, University of Calgary, Zucker Hillside Hospital, University of California – San Francisco (UCSF), and the University of California – Los Angeles (UCLA) (Author et al., 2012). NAPLS 2 was initiated in 2007 with the goal of collecting more extensive biological data from a larger CHR population and with the aim of testing the predictive conversion algorithm developed through NAPLS 1 as well as some specific hypotheses about neural mechanisms in conversion (Addington et al., 2012). This study was funded by the National Institute of Mental Health (NIMH) and was conducted over the course of five years, ending in 2012.

Sample

A total of 764 CHR and 280 healthy control individuals were recruited in NAPLS 2 (Addington et al., 2015). Individuals between 12 and 35 years old were included in the study. Exclusion factors included any current diagnosis of a psychotic disorder, substance dependence in the past 6 months, an IQ below 70, history of any central nervous system disorder, and current use of psychotropic medication (Addington et al., 2012). In order to be eligible to participate as a member of the CHR group, individuals needed to meet prodromal criteria as outlined in Criteria

of Prodromal Symptoms (COPS) as described below (McGlashan et al., 2010; cited in Addington et al., 2015).

The subsample included in the present study was 390 CHR individuals and 179 healthy controls, for whom data on both nicotine use and symptoms were collected at baseline. Of these individuals, 210 CHR individuals also had data available at the 12-month follow up visit. Due to subject attrition, missing follow-up visits, or conversion to psychosis, there were fewer subjects available at the 12-month follow up visit. Substance use in healthy control individuals was assessed at baseline and compared to substance use in CHR individuals in order to determine any differences in substance use between the diagnostic groups.

Individuals aged 17 years old or younger were excluded from analyses due to the inability of these individuals to legally buy cigarettes (and thus greatly reduced rates of smoking). As SES is known to be a factor linked with smoking behavior, its relation with substance use and symptoms was also examined (Barbeau, Krieger, & Soobader, 2004).

Measures

Structured Interview for Prodromal Symptoms (SIPS)

The Structured Interview for Prodromal Symptoms (SIPS) was administered to all participants. It yields diagnoses for several prodromal syndromes. An individual may meet as CHR through one of three ways: Brief Intermittent Psychotic Syndrome (BIPS), Genetic Risk and Deterioration (GRD), and Attenuated Positive Symptom Syndrome (APSS) (Addington et al., 2015). An individual may meet criteria for BIPS if they have experienced at least one positive symptom of psychosis at a psychotic level for an amount of time less than that required for a diagnosis of psychosis in the past three months (Author et al., 2012). In order to meet criteria through GRD, an individual must have schizotypal personality disorder or a first-degree

relative with a psychotic disorder in addition to having experienced a significant decline in functioning within the past month (Addington et al., 2015). Finally, inclusion through APSS would require that the individual experience an attenuated positive symptom (such as suspiciousness or perceptual abnormalities) at least once a week with a noted increase in severity (below the threshold for psychosis) within the last year (Addington et al, 2015). Subjects that met criteria to participate either in the CHR or healthy control groups were brought in for assessments every six months, ending after 24 months or conversion to psychosis.

The Structured Clinical Interview for DSM-IV (SCID-IV)

This measure was used in order to diagnose current psychiatric disorders (Addington et al., 2015; First, Spitzer, Gibbon, Williams, B., & Williams, J., 1995). Subjects were assessed for inclusion as CHR participants with the SIPS. Each prodromal symptom was rated on a seven-point scale on the Scale of Prodromal Symptoms (SOPS), with a score of "0" indicating that the symptom was not present and a score of "6" indicating that the symptom was present at a psychotic level of severity (McGlashan et al., 2010). Scores were obtained for positive, negative, disorganized (i.e., bizarre thinking), and general (i.e., dysphoric mood and motor disturbances) symptoms. In particular, and relevant to the current study, a total of six negative symptoms were rated – Social Anhedonia (N1), Avolition (N2), Expression of Emotion (N3), Experience of Emotions and Self (N4), Ideational Richness (N5), and Occupational Functioning (N6).

Substance abuse was assessed using the Alcohol and Drug Use Scale (Drake, Mueser, & McHugo, 1996). Raters assessed both current dependence and frequency of use within the past month. Current dependence was rated on a scale of 1-5, with a score of "1" indicating no use of the indicated substance during the past month and a score of "5" indicating severe dependence and/or hospitalization. Frequency of use for marijuana and alcohol was measured by in

categories ranging from 0 to 5, with "0" indicating no use, "1" indicating use once or twice per month, "2" indicating use 3-4 times per month, "3" indicating use 1-2 times per week, "4" indicating use 3-4 times per week and "5" indicating nearly daily usage. For cigarette use, the frequency variable was coded differently, with scores ranging from 1 to 4 and varying depending on the number of cigarettes smoked on a daily basis. A score of "1" indicated occasional use, a score of "2" indicated less than 10 cigarettes smoked per day ("moderate" use), a score of "3" indicated that between 11 and 25 cigarettes were smoked each day, and a score of "4" indicated that over 25 cigarettes were smoked on a daily basis within the last month.

Analytical Strategy

All analyses were conducted using SPSS version 23. As previously stated, all subjects aged 17 years old or younger were excluded from analyses due to potential confounds and general lack of smoking in this age group.

Prior to analysis, descriptive statistics on group demographic factors were derived and group comparisons were conducted. See Table 1 for demographic factors by diagnostic group and nicotine use.

Ordinal regression was used in order to determine the significance of smoking frequency in predicting negative symptom severity. Only the frequency variables (rated from 0-4 for nicotine and 0-5 for marijuana and alcohol) for all substances were included in analyses. Because very few individuals were rated as having a frequency score of 3, groups rated at a 3 or 4 in the nicotine category were collapsed into a single "heavy daily smokers" group. Analyses with each of the six negative symptoms as well as overall mean negative symptom severity (computed by averaging an individual's score on the individual negative symptoms) as dependent variables were conducted. These sets of analyses were conducted twice, using

concurrent substance use data – once for data collected at baseline, and once for data collected at the 12-month follow-up visit.

After this, repeated measures analyses of covariance were performed in order to assess whether CHR individuals experienced a change in symptom severity over time as a function of baseline nicotine use. These analyses were performed on mean overall negative symptom score and each individual negative symptom.

Finally, baseline ordinal regression analyses were conducted one additional time with the addition of an interaction term for sex and nicotine. This was done in order to explore the possible interaction of sex and nicotine due to the different areas of the brain in males and females in which dopaminergic activity has been found as a result of cigarette use (Cosgrove et al., 2014).

Results

The means and standard deviations for demographic factors, and rates of use of psychotropic and recreational drugs are listed in Table 1 by diagnostic group and nicotine use. As mentioned, due to the high levels of comorbidity among types of substance use, rates of marijuana and alcohol use by nicotine use are listed by diagnostic group in Table 1. Psychotropic medication use rates for antipsychotics, antidepressants, stimulants, and anticonvulsants are also shown.

Preliminary Analyses -

Control variables for subsequent analyses were determined based on the group differences observed in Table 1. Chi-square tests of independence were performed in order to determine whether there were any significant relationships between nicotine group and other substance use, medication use, and sex. Results for healthy control individuals indicate that

marijuana use is significantly related to nicotine use, χ^2 (3, N = 174) = 10.92, $p < .05$, such that individuals who use one are more likely to use the other. Marijuana use was also significantly related to nicotine group in CHR individuals, χ^2 (3, N = 374) = 40.35, $p < .01$. Alcohol use was significantly related to nicotine group in CHR individuals, χ^2 (3, N = 374) = 20.89, $p < .01$. Due to the significance of these preliminary analyses, marijuana and alcohol use were included as control variables in subsequent analyses.

Medication use was not significantly related to nicotine group in chi-square analyses conducted in both diagnostic groups, so these variables were not included as control variables in subsequent analyses. However, sex was included as a control variable, as chi-square analyses found that it was significantly related to nicotine group within the CHR diagnostic group, χ^2 (3, N = 374) = 8.18, $p < .05$, with more males (37.4%) reporting smoking behavior than females (24.5%). This variable is additionally appropriate to include as a control variable as it has been noted in the literature that male individuals typically exhibit more severe negative symptoms and tend to smoke more cigarettes on a daily basis than females (Sisek-Šprem et al., 2015; Thompson et al., 2015). Complete information regarding the results of preliminary analyses on medication and substance use can be found in Table 1.

Additionally, analyses conducted with a one-way analysis of variance found that the mean age of each nicotine group did not differ within the CHR sample, $F(3, N = 374) = 1.22$, $p = .301$. However, the mean age among nicotine groups did differ in the healthy control sample, $F(3, N = 174) = 3.23$, $p < .05$. Tukey post hoc analyses found that the mean ages of healthy controls in nicotine groups “1” (occasional smokers) and “2” (moderate smokers) differed significantly (4.87, 95% CI [0.00-9.74], $p < .05$), while the mean age of individuals in the other nicotine groups did not differ significantly from any other group. However, as no significant

difference in mean age was found in the CHR sample, age was not included as a control variable in subsequent analyses.

SES was also examined due to the known relationship between this factor and smoking behavior. Chi-square tests of independence were conducted on nicotine and SES for both the diagnostic groups and results indicate that SES is not significantly related to nicotine use in either the CHR (χ^2 (18, N = 372) = 13.71, $p > .05$) or the healthy control groups (χ^2 (18, N = 173) = 19.80, $p > .05$). Therefore, SES was not included as a control variable in subsequent analyses.

Finally, Spearman's correlations were conducted in order to determine whether nicotine use category was related to frequency of use (instead of whether an individual is simply a user or a non-user) in both alcohol and marijuana. Again, these categories ranged from 0-5 for frequency of use for marijuana and alcohol. No category for either substance contained fewer than 10 individuals; thus, no categories were collapsed before analysis. Results indicated that frequencies of use for both marijuana (r_s =.169, $p < .05$) and alcohol (r_s = .253, $p < .01$) were significantly and positively correlated with nicotine use in the healthy control group. Likewise, frequencies of use for marijuana (r_s = .321, < .01) and alcohol (r_s = .274, $p < .01$) were significantly and positively correlated with nicotine use in the CHR group. Thus, the frequencies of use (rather than simply presence of use) for both substances were included as control variables in all subsequent analyses. Information regarding these analyses is listed in Table 2.

Baseline Analyses

Ordinal logistic regression was performed first on the cumulative mean negative score (obtained by averaging the scores of each of the six individual negative symptoms; see Figure 1) for the baseline data for CHR individuals. Although symptom scores were initially rated from 0-

6, no individuals had a mean score of six and only one individual had a mean score of five, necessitating the collapse of this group into the group of individuals with a mean score of 4. The distribution for this new mean score variable was approximately normal, with most individuals having a mean score of 2. Multicollinearity in the data was assessed before analysis and was not found to be present. Additionally, results from a full likelihood ratio test indicated that there were proportional odds, $\chi^2 = 20.69$, $p = .30$. Comparisons of each nicotine group (non-smokers, occasional smokers, moderate smokers, and heavy smokers) were produced in order to assess significant differences in the predictive validity of one nicotine group in relation to another nicotine group. Alcohol, marijuana, and sex were additionally included in the model as covariates. The results from this analysis can be found in Table 3. Results indicate that nicotine group is not a significant predictor of mean negative symptom severity and that sex and marijuana are also not significant predictors of mean negative symptom severity. However, an increase in alcohol frequency was significantly associated with a decrease in the odds of having a higher mean negative symptom score, with an associated odds ratio of 0.85, 95% CI [0.74, 0.97], χ^2 (1) = 5.64, $p < .05$. The model was found to be a good fit to the data with a deviance goodness-of-fit test, χ^2 (696) = 376.82, $p = .99$; however, most cells (as assessed by combination of covariate patterns by levels of dependent variable) were scarce. Overall, the model significantly predicted mean negative symptom score, χ^2 (6) = 12.71, $p < .05$.

Following this, ordinal regression analyses were performed on each of the six individual negative symptoms with the nicotine group included as the predictor variable and sex, alcohol, and marijuana included as covariates. These symptoms were rated from 0-6, with a score of "0" indicating that the symptom was not present and a score of "6" indicating extreme severity. Prior to analysis, the *n* for each symptom score was assessed in order to determine that an adequate

number of individuals was present in each group. Due to low group numbers, the highest scoring group of individuals for decreased expression of emotion and decreased ideational richness was collapsed with the next highest scoring group. Multicollinearity was again assessed before analysis and found to not be present. The results from each of these analyses can be seen in Tables 4 and 5, with Table 4 providing regression coefficients for the predictor nicotine and Table 5 providing regression coefficients for the covariates. Additionally, full likelihood ratio tests produced for each analysis indicated that the assumption of proportional odds had been met ($p > .05$), with the exception of the analysis performed on experience of emotions and self, which indicated a potential violation of this assumption ($p < .05$).

Results from the analysis performed on social anhedonia indicate that CHR individuals that smoke moderately were significantly more likely to have a lower symptom score (ie., less social anhedonia) than those who did not smoke, with an odds ratio of 0.54, 95% CI [0.31, 0.96], χ^2 (1) = 4.37, $p < .05$. No other nicotine group comparison was significant in this analysis. Results also indicated that an increase in frequency of alcohol usage was associated with a lower social anhedonia score, with an odds ratio of 0.84, 95% CI [0.73, 0.96], χ^2 (1) = 6.76, $p < .05$. However, sex and alcohol were not found to be significant predictors in this model. A deviance goodness-of-fit test found this model to be a good fit to the data, χ^2 (696) = 498.22, $p = 1.00$; however, most cells were scarce. The overall model significantly predicted the symptom score for social anhedonia, χ^2 (6) = 673.77, $p < .01$.

Nicotine was additionally found to be a significant predictor in the analysis performed on decreased occupational functioning. Individuals that did not smoke were significantly more likely to have a lower occupational functioning score (ie., better occupational functioning) than those who smoke heavily, with an odds ratio of 0.49, 95% CI [0.25, 0.96], χ^2 (1) = 4.39, $p < .05$.

Individuals that smoke occasionally were also significantly more likely to have a lower symptom score than heavy smokers, with an odds ratio of 0.35, 95% CI [0.15, 0.80], χ^2 (1) = 6.23, $p < .05$. Additionally, individuals that smoke occasionally were significantly more likely to have a lower symptom score than those who smoked moderately, with an odds ratio of 0.38, 95% CI [0.18, 0.81], χ^2 (1) = 6.33, $p < .05$. Finally, moderate smokers were significantly more likely to have a higher symptom score than those who did not smoke, with an odds ratio of 1.85, 95% CI [1.05, 3.27], χ^2 (1) = 4.54, $p < .05$. Alcohol was again found to be a significant predictor of lower symptom score, with an odds ratio of 0.81, 95% CI [0.71, 0.93], χ^2 (1) = 9.06, $p < .01$. This model was found to be a good fit to the data, with a deviance goodness-of-fit test of χ^2 (696) = 529.71, $p = 1.00$; however, most cells were scarce. The overall model significantly predicted the symptom score for occupational functioning, χ^2 (6) = 20.02, $p < .01$.

Nicotine was not a significant predictor of symptom score in analyses performed on the remaining negative symptoms. However, several covariates significantly predicted symptom score in these models. Alcohol was again found to be a significant predictor of lower symptom score in ideational richness (ie., greater ideational richness), with an odds ratio of 0.84, 95% CI [0.73, 0.97], χ^2 (1) = 5.50, $p < .05$. Sex was also found to be a significant predictor in this model. Males had significantly highly odds of having a higher symptom score, with an odds ratio of 1.71, 95% CI [1.14, 2.58], χ^2 (1) = 6.72, $p < .05$. A deviance goodness-of-fit test indicated that this model was a good fit to the data, χ^2 (462) = 347.44, $p = 1.00$; however, most cells were scarce. The overall model significantly predicted ideational richness symptom score, χ^2 (6) = 13.68, $p < .05$. Males were also significantly more likely to have a higher symptom score in expression of emotion (ie., less expression of emotion), with an odds ratio of 1.61, 95% CI [1.09, 2.38], $\chi^2 = 5.65$, $p < .05$. The model was found to be a good fit for the data, with a deviance

goodness-of-fit test of χ^2 (579) = 420.88, p = 1.00; however, most cells were scarce and the overall model did not significantly predict symptom score in expression of emotion, χ^2 (6) = 562.14, p = .20.

The mean symptom score (adjusted for the influence of covariates sex, marijuana, and alcohol) of each nicotine group for each negative symptom was obtained through multiple analysis of covariance and can be seen in Figure 2.

12-Month Analyses

The analyses performed on CHR data at baseline were also conducted on data available at the 12-month follow-up visit; however, these analyses were performed using the substance use data collected at the 12-month visit. Again, the number of individuals for which data was available at this time point (n = 210) was smaller than at baseline. A mean overall negative symptom score variable was computed (see Figure 3) for the first analysis. Unlike the distribution of the mean score at baseline, however, the distribution of this mean score is not normal and appears to have positive skew, with the majority of individuals having a mean score of 1. Multicollinearity was assessed before analysis and was not found to be present. Additionally, a full likelihood ratio test indicated that the assumption of proportional odds had not been violated in this analysis, χ^2 (18) = 18.38, p = .43. However, unlike at baseline, neither nicotine group nor covariate variable was a significant predictor of mean negative symptom score (see Table 6).

Next, ordinal regression analyses were run on each individual negative symptom. The results from each of these analyses can be seen in Tables 7 and 8, with Table 7 providing regression coefficients for the predictor nicotine and Table 8 providing regression coefficients for the covariates. Prior to analysis, the n for each symptom score was assessed in order to

determine that an adequate number of individuals was present in each group. Due to low group numbers, the highest scoring group of individuals for social anhedonia, avolition, decreased expression of emotion and self, and decreased ideational richness was collapsed into the next highest scoring group. Multicollinearity was assessed before analysis and was not found to be present. Full likelihood ratio tests produced for each analysis indicated that the assumption of proportional odds had been met ($p > .05$), with the exception of the analysis performed on avolition, which indicated a potential violation of this assumption ($p < .05$). As in the baseline analysis, moderate smokers were significantly less likely to have social anhedonia symptoms than those who do not smoke, with an odds ratio of 0.21, 95% CI [0.09, 0.47], χ^2 (1) = 14.42, $p <$ .01. This relationship appears to be stronger than that seen at baseline, with a lower odds ratio than in the baseline analysis (0.54) and a lower *p*-value. Alcohol was likewise also still a significant predictor of lower symptom score, with an odds ratio of 0.79, 95% CI [0.66, 0.94], χ^2 (1) = 6.83, $p < .05$. A deviance goodness-of-fit test indicated that the model was a good fit to the data, although cells were scarce. The overall model significantly predicted symptom score, χ^2 (6) = 32.99, $p < .01$.

However, unlike results found at baseline, nicotine group was not a significant predictor of symptom severity in occupational functioning. Alcohol was likewise no longer a significant predictor of this symptom. Additionally, nicotine was not a significant predictor of the severity of any other negative symptom at the 12-month follow-up visit.

Alcohol was also a significant predictor of lower symptom score in ideational richness, with an odds ratio of 0.76, 95% CI [0.63, 0.93], χ^2 (1) = 7.12, $p < .05$. A deviance goodness-of-fit test indicated that this model was a good fit to the data, χ^2 (306) = 193.12, $p = 1.00$; however,

most cells were scarce. The overall predictive validity of the model was trending towards significance, χ^2 (6) = 12.61, p = .05.

Males were significantly more likely than females to have a higher symptom score in expression of emotion, with an odds ratio of 1.94, 95% CI [1.11, 3.39], χ^2 (1) = 5.34, p < .05. Although a deviance goodness-of-fit test indicated that the model was a good fit for the data, χ^2 (305) = 221.47, p = 1.00, most cells were scarce and the overall predictive validity of the model was not significant, χ^2 (6) = 8.48, p = .21.

As in the baseline analyses, the mean symptom score of each nicotine group for each negative symptom, adjusted for covariates, was obtained through multiple analysis of covariance and can be seen in Figure 4.

Repeated Measure Analyses

Next, repeated measure analyses of covariance were performed on all subjects at baseline that had available data for the 12-month visit (n = 210) in order to determine whether baseline nicotine use was related to a change in symptom severity over time. These analyses were performed using a within-subjects factor consisting of two levels – baseline symptom score and 12-month symptom score. Baseline nicotine use was included in each model as a between-subjects factor, with marijuana, alcohol, and sex included additionally as covariates. This analysis was first performed on mean overall negative symptom score. Examination of studentized residuals indicated that there were no outliers, as there were no values ± 3. Results of a Normal Q-Q plot indicated some potential deviation from normality, however. The results of Levene's test for equality of variances and Box's M test indicated that there was homogeneity of variances and covariances (p > .05). Results of the analysis indicate no significant interaction of nicotine and symptom change over time, F(3, 198) = 0.90, p = .44, partial η^2 = .01. Results from

this test can be found in Table 9; additionally, change in symptom severity over time as a function of nicotine use at baseline was plotted and can be seen in Figure 5.

Next, repeated measure analyses of covariance were performed for each individual negative symptom, with the within-subjects factor again consisting of baseline symptom score and 12-month symptom score and the between-subjects factor being nicotine use at baseline (in addition to the inclusion of marijuana, alcohol, and sex as covariates). Examination of studentized residuals for social anhedonia indicated that there were no outliers present. Results of a Normal Q-Q plot indicated some potential deviation from normality. Additionally, results from Box's M test indicate a potential lack of homogeneity of covariance ($p < .05$). However, Levene's test for equality of variances indicated homogeneity of variances ($p > .05$). No significant interaction of nicotine and symptom change over time was found, $F(3, 199) = 0.84$, $p = .48$, partial $\eta^2 = .01$. However, sex was found to be significant in this analysis, $F(1, 199) = 5.70$, $p < .05$, partial $\eta^2 = .03$. Results from this test can be found in Table 9; additionally, change in social anhedonia severity over time as a function of baseline nicotine use was plotted and can be seen in Figure 6.

Neither nicotine nor any covariate variable was found to be significant in the analyses on the remaining individual negative symptoms. The results from these tests can be seen in Table 9. Figures for nicotine use and symptom change over time for each of these analyses were also created (See Figures 7 through 11).

Exploratory Analyses – Interaction between Nicotine and Sex

Baseline ordinal regression analyses were run again with the addition of an interaction variable between sex and nicotine use. These analyses were run first on overall mean negative symptom score and then on each individual negative symptom score. Results from the analysis

performed on mean overall negative symptom score indicated that there was a significant interaction of nicotine and sex in occasional smokers as compared to non-smokers. Occasional smokers (with an interaction with sex) had a significantly lower chance of having more severe overall symptoms, with an odds ratio of 0.20, 95% CI [0.05, 0.82], χ^2 (1) = 5.01, $p < .05$. A deviance goodness-of-fit test indicated that this model was a good fit to the data, χ^2 (459) = 371.21, $p = 1.00$; however, most cells were scarce. The overall model significantly predicted mean symptom score, χ^2 (9) = 18.31, $p < .05$. A full likelihood ratio test indicated that the assumption of proportional odds had been met ($p > .05$). Results from this analysis can be seen in Table 10.

Interaction terms were also found to be significant in analyses performed on social anhedonia and experience of emotions and self. Results for social anhedonia were similar to those found for overall mean negative symptom score, in that the interaction term for occasional smokers was found to have a significantly lower chance of having more severe social anhedonia than non-smokers, with an odds ratio of 0.23, 95% CI [0.06, 0.94], χ^2 (1) = 4.23, $p < .05$. A deviance goodness-of-fit test indicated that this model was a good fit to the data, χ^2 (693) = 493.620, $p = 1.00$; however, most cells were scarce. The overall model significantly predicted mean symptom score, χ^2 (9) = 669.17, $p < .05$. A full likelihood ratio test indicated that the assumption of proportional odds had been met ($p > .05$).

Results for the analysis performed on experience of emotions and self indicated that the interaction term for moderate smokers had a significantly lower chance of having more severe (e.g., decreased) experience of emotion and self as compared to the interaction term for occasional smokers, with an odds ratio of 0.15, 95% CI [0.03, 0.88], χ^2 (1) = 4.44, $p < .05$. A deviance goodness-of-fit test indicated that this model was a good fit to the data, χ^2 (576) =

462.97, p = 1.00; however, most cells were scarce. The overall model did not significantly predict mean symptom score, χ^2 (9) = 620.64, p = .28. A full likelihood ratio test indicated that the assumption of proportional odds had been met (p > .05). Results from analyses on each individual negative symptom can be seen in Table 11.

Discussion

Rates of Substance Use and Preliminary Analyses

As hypothesized, CHR individuals exhibited a much higher rate of smoking than healthy controls, with 35% of CHR individuals reporting some smoking behavior (as measured simply by presence of use instead of by nicotine group) and only 13% of healthy controls reporting smoking behavior. This rate of smoking is consistent with that found in the literature review conducted by Addington et al. (2014), which reported rates of nicotine use ranging from 16-34% in CHR populations recruited in past studies. Additionally, as hypothesized, although rates of smoking in CHR population were elevated as compared to healthy controls, this smoking rate was not as high as that typically seen in psychotic populations (which can be around 75% or higher) (Berg et al., 2013).

CHR individuals also reported using marijuana at a much higher rate than healthy controls, with 26% of CHR individuals reporting marijuana use but only 12% of healthy controls. This is consistent with previous findings and also important in light of the ever-increasing body of research linking marijuana use to the prodromal phase and the onset of psychosis (Comptom et al., 2009). Interestingly enough, the healthy control sample used alcohol at a higher rate than the CHR population, with 71% of control individuals reporting alcohol use as opposed to 58% of CHR individuals. These findings are contrary to past reports, which indicate that CHR or psychotic individuals abuse substances at a higher rate than the general

population (Addington et al., 2014). However, these differences in alcohol use are likely attributable to age, as the mean age of the present CHR group (as seen in Table 1) is lower (around 21 years of age) than the mean age of the healthy control group (which trends above the legal age required to buy alcohol).

Further, there does appear to be a higher rate of use of multiple substances among individuals in the CHR group compared to those in the healthy control group. 71% of marijuana users and 84% of alcohol users in the healthy control group did not report any nicotine use, while only 45% of marijuana users and 58% of alcohol users in the CHR group reported no nicotine use. Additionally, although use of both marijuana and alcohol was significantly related to nicotine usage in the CHR sample ($p < .00$), marijuana was not significantly related to nicotine usage in the healthy control sample ($p > .05$). Although not examined in depth in the current study (i.e., the concurrent use of alcohol with marijuana or with other substances was not examined), this would suggest higher rates of concurrent substance abuse in the CHR sample. This is consistent with previous research findings, which have indicated high rates of comorbidity of substance abuse in both prodromal and psychotic individuals (Margolese et al., 2004; Meszaros et al., 2011). The significant relationship between nicotine use and sex found in the CHR sample is also consistent with previous research findings, which indicate a greater rate of daily smoking among male individuals (Thompson et al., 2015).

It is surprising that there was no relationship between nicotine use and medication use. Past research findings have indicated a positive association between smoking and the use of some antipsychotics, likely due to the role that these antipsychotics have in partially blocking dopamine-producing nicotinic receptors in the brain (Meszaros et al., 2011). The lack of such a relationship in the current study could be explained simply by the low use of antipsychotics in

this CHR sample, as only 47 CHR individuals reported antipsychotic use out of the 390 of those aged 18 years or older who had baseline data available. It should also be noted that the majority of past studies examining this relationship utilized study samples consisting of individuals who were already psychotic and thus likely had been using antipsychotics for a longer period of time and with greater frequency than the CHR individuals in the current study.

Nicotine Use at Baseline

It was hypothesized that the severity of negative symptoms of CHR individuals at baseline would be positively associated with frequency of nicotine use (as measured by number of cigarettes smoked). However, analyses performed on overall mean negative symptom score indicated there was no significant relationship between nicotine use and mean negative symptom score. Additionally, nicotine was not associated with negative symptom scores in four of the six negative symptoms measured in the current study. However, nicotine use was positively associated with increased deficits in occupational functioning. Significant differences in occupational functioning were found when comparing those groups that differed most in rate of smoking (e.g., non-smokers and those who smoked moderately) instead of those most similar (e.g., non-smokers and occasional smokers or moderate and heavy smokers). This would support the hypothesized positive relationship between nicotine use and severity of impairment in occupational functioning. In addition, this relation is not attributable to sex or to use of other substances, as nicotine is significant with the inclusion of control variables (sex, marijuana, and alcohol). When considering the mean symptom scores for each level of nicotine usage (Figure 2), the mean symptom score of avolition for heavy smokers is significantly higher than for non-smokers. Although this relationship was not similarly significant in ordinal analyses, it is

interesting to consider in that it closely resembles the findings for impairment in occupational functioning.

Nicotine was also a significant predictor in the analysis of social anhedonia – however, in this analysis, moderate nicotine use (specifically only as compared to those who did not smoke cigarettes) was predictive of a lower symptom score. This is contrary to the hypothesized positive relationship between the two variables, but consistent with some evidence that moderate substance use is linked with greater social connections in youth. Specifically, Bond et al. (2007) conducted a study investigating the relationship between social connectedness in youth and later substance use and mental illness and found that individuals in the study with a high level of social connectedness (as measured by whether an individual had secure and trusting friendships) had a higher likelihood of becoming regular smokers of both cigarettes and marijuana than those who had poor social connectedness. Thus, it is possible that the observed inverse relationship between greater levels of social anhedonia and moderate nicotine use is due to greater social connectedness in this particular subset of CHR individuals.

Although not significant in the main ordinal analyses, it appears that the mean symptom score for experience of emotions and self (Figure 2) for occasional smokers is significantly higher than for moderate smokers. This trend is similar to that found in social anhedonia, in that a group with a higher level of smoking exhibited significantly less severe symptoms than a group with a lower level of smoking. It is possible for this reason that this symptom is also related to social connectivity in that increased experience of emotions and self is positively related to social connectedness and thus related to a greater likelihood of later substance use.

Nicotine Use at the 12-Month Visit

As in the baseline analyses, nicotine was not predictive of the severity of overall mean negative symptom score. This is contrary to hypotheses, which predicted a positive relationship between 12-month nicotine use and symptom severity at the 12-month follow-up visit. Additionally, nicotine was not a significant predictor of severity for five of the six individual negative symptoms. Although baseline nicotine use significantly predicted the severity of impairment in occupational functioning at baseline, 12-month nicotine use did not significantly predict severity of impairment at the 12-month visit. This change in significance could be the result of a number of different factors. It could be partially the result of a lower number of participants for which data was available at the 12-month visit (n = 210 as opposed to n = 390 at baseline). Additionally, this could also partially be a result of the general tendency of negative symptoms to improve over time in CHR samples (excluding those that later convert to psychosis, who typically have more persistent and severe negative symptoms) (Piskulic et al., 2012). Finally, it is likely that there was a change in frequency of nicotine use in individuals over time that was not accounted for in these analyses.

However, nicotine remained a significant predictor of severity of social anhedonia at 12 months. The same comparison found to be significant in baseline analyses was also significant in these analysis – those individuals who smoked moderately had significantly lower social anhedonia compared to those who reported no smoking. In fact, this relationship appears to be stronger than seen at baseline. Moderate smokers were more likely to have a lower score at the 12-month visit than they were at baseline (as interpreted based on the lower odds ratio found in the 12-month analyses). Additionally, when considering the mean symptom scores from baseline (Figure 2) and at 12 months (Figure 4), it appears that there is a growing difference between moderate and heavy smokers, in which heavy smokers have higher levels of negative symptoms

than moderate smokers. Although a heavy level of smoking was neither predictive of social anhedonia at baseline or at 12 months and was additionally not significantly different in mean score from a moderate level of smoking at either time-point, it is interesting that these individuals have higher levels of social anhedonia than moderate smokers. This is suggestive of a potential non-linear relationship between smoking and social anhedonia. As the overall model was a significant predictor of the severity of this symptom, it can be assumed that nicotine is a significant predictor independent of covariates.

Although contrary to the predicted positive relationship between nicotine usage and symptom severity, this relationship is interesting in its persistence (and apparent strengthening) over time in the CHR sample. One potential explanation for this relationship could be found in the neurobiological role of nicotine. Nicotine has been shown to stimulate neural reward systems in animal models – Kenny and Markou (2006) found that rats that self-administered nicotine exhibited a sensitization of reward systems that persisted for up to 36 days after nicotine access had been removed and, furthermore, that the sensitivity of these reward systems had been permanently increased. Social anhedonia is considered to be a result, in part, of deficits in the reward systems of the brain (Der-Avakian & Markou, 2012). It is possible that the observed relationship between moderate levels of daily smoking and lower levels of social anhedonia is due, in part, to the sensitization of the reward systems produced by nicotine usage in these individuals. However, it is not possible to draw conclusions of causal relationships from the current study, as no experimental manipulation was present that would allow for such an interpretation.

Another likely explanation could be found in nicotine's role in social settings. As before stated, individuals with greater levels of social connectedness have been found to have a higher

likelihood of becoming regular smokers later in life (Bond et al., 2007). This explanation appears more plausible than the alternative, in which social anhedonia is alleviated by nicotine use. Thus, it is perhaps the case in this sample that individuals with higher levels of social anhedonia do not smoke because their symptoms prevent them from seeking out the social connections and situations in which this behavior would be more likely to occur. Likewise, it is also possible that individuals with heavy levels of smoking are more impaired in their symptom presentation than their moderately-smoking counterparts.

Nicotine and Repeated Measures Analyses

Contrary to hypotheses, nicotine use at baseline was not related to symptom change over time. This is surprising, given that the results of the analysis on concurrent 12-month nicotine use and symptom severity indicated potentially lower symptom severity in moderate smokers as compared to occasional smokers than found when examining the same relationship with concurrent baseline nicotine use and symptom severity. The fact that this relationship was not found in the repeated measures analyses using only baseline nicotine use suggests that there is also a change in nicotine use over time in this CHR population that should be taken into account when examining the results of the concurrent 12-month ordinal regression analyses.

Additionally, as can be seen when viewing the figures produced from these analyses (Figures 5 through 11), it appears that members of each nicotine group tend to experience some decrease in symptom severity over time. This is contrary to the hypothesis that nicotine users would experience a decrease in symptom severity over time when compared to non-users.

Exploratory Analyses - Interaction between Nicotine and Sex

Exploratory ordinal regression analyses including an interaction term between nicotine and sex indicate that, overall, there does not appear to be an interaction between sex and nicotine

in predicting negative symptom severity in CHR individuals. However, it does appear as if at least one interaction comparison was significant in the analyses on overall mean negative symptom severity, social anhedonia, and experience of emotions and self. The overall model for experience of emotions and self was not significant; however, the models for social anhedonia and overall negative symptom severity were significant and indicate that there is an interaction of sex at the occasional level of nicotine use as compared to no nicotine use that significantly decreases the chance of these individuals having higher impairment in social anhedonia and overall symptom severity. This indicates that there are differences in symptom severity based on sex at these particular levels of nicotine use. These findings may, in part, be explained by the different ways in which males and females react to the nicotine in cigarettes (Cosgrove et al., 2014). Cosgrove et al. (2014) found that male and female brains respond differently in the ways in which they produce dopamine as a reaction to cigarette use – specifically, men tend to show a dopaminergic response in the ventral striatum, but women tend to show a response in the dorsal putamen. These findings support reported sex differences in reasons individuals smoke, in that men typically smoke due to the reinforcement from the effects of nicotine and that women typically smoke for a number of other reasons, such as stress reduction (Cosgrove et al., 2014). It is possible that these differing regions of dopaminergic activity and differing reasons for smoking have some relation to the results of these exploratory analyses; however, more in-depth analyses regarding the nature of these relationships (e.g., in regards to the exact differences in symptom severity based on sex at each level of nicotine use) would have to be conducted.

Alcohol, Marijuana, and Sex

Alcohol use was inversely associated with overall mean negative symptom severity at baseline, as well as with the severity of social anhedonia, decreased ideational richness, and

impaired occupational functioning. Specifically, alcohol use was associated with less impairment in each of these areas and with a lower overall mean symptom score. However, 12-month alcohol use did not significantly predict overall mean symptom severity or severity for any individual negative symptom at the 12-month follow-up visit.

It is interesting to find that alcohol is related to both individual symptoms and overall mean symptom severity at baseline. Past studies have reported finding an inverse relationship between negative symptom severity scores and alcohol use in psychotic individuals (Batki, Leontieva, Dimmock, & Ploutz-Snyder, 2008). Batki et al. (2008) found such an inverse relationship in a population of psychotic (or psychosis-spectrum) individuals with co-occuring alcohol use disorder or alcohol abuse and attributed their findings to a potential inability to experience alcohol-related rewards, such as an alcohol "high" or euphoria, in addition to reduced craving for the substance. Additionally, a meta-analysis of past research findings conducted by Talamo et al. (2006) found that diagnosis of comorbid substance use disorders was associated with a lower severity of negative symptoms. Apparent absence of this relationship at the 12-month visit could, again, be explained by the reduced statistical power due to the lower number of participants and by the overall tendency of negative symptoms in prodromal populations to decrease over time (Piskulic et al., 2012). It is likely that there was additionally some change in alcohol use over time not accounted for in these analyses; however, repeated measures analyses confirmed that baseline alcohol use was not related to symptom severity over time.

Sex was found to be significant in predicting severity of impairment in both expression of emotion and ideational richness at baseline. Specifically, males were more likely to have higher symptom scores than females. These findings are consistent with past research indicating that males typically exhibit more severe negative symptoms than females (Sisek-Šprem et al., 2015;

Thompson et al., 2015). However, the overall models for these symptoms were not predictive of symptom severity, indicating that, in this sample, sex is not predictive of symptom severity when the influence of other covariates is assessed concurrently. As with alcohol, sex was no longer predictive of symptom severity at the 12-month follow-up visit. Again, this could be attributed to a lower number of participants at this time-point, as well as the overall decreasing trend of negative symptoms (Piskulic et al., 2012).

Additionally, sex was related to social anhedonia symptom severity over time. Although sex was not significant in any other repeated measures analysis, this is an interesting finding that would warrant further investigation. Males typically have higher levels of negative symptom severity than females; it is possible, then, that this relationship persists over time in CHR individuals and that males experience less of a decrease in symptom severity than females (Sisek-Šprem et al., 2015). However, more investigation into the relationship found in this analysis would have to be conducted in order to establish the nature of this relationship.

Limitations

Limitations of the current study include the lack of experimental manipulation necessary to draw causal inferences regarding the role of nicotine in CHR symptom presentation. Thus, any inferences about causality must be considered tentative. Additionally, as before been mentioned, there were a lower number of data available at the 12-month follow-up visit due to subject attrition (e g., conversion to psychosis, or inability to attend assessments).

Additionally, only one aspect of the self-medication hypothesis of nicotine was examined in the current study. Specifically, the current study examined only the potential relationship between nicotine use and negative symptom severity proposed in past research studies (Kumari & Postma, 2005). The self-medication hypothesis does not address solely the negative symptoms

of schizophrenia but rather addresses a wide variety of symptoms related to psychotic disorders. Future studies should investigate other factors, such as cognitive deficits, that could potentially be related to nicotine use.

Conclusions

In conclusion, the present study finds little evidence supporting the self-medication theory of nicotine use as it applies to the negative symptoms of schizophrenia in CHR individuals. Instead, it appears that CHR patients who smoke in moderation have lower social anhedonia. Therefore, symptoms may be determining smoking behavior, rather than nicotine use acting as self-medication. Although there is an observed decrease in negative symptom severity over time in the current sample, there is no evidence to suggest that this is due to the influence of nicotine. The exception to this trend is the positive relationship between deficits in occupational functioning, increased levels of avolition and nicotine use, which is evident at baseline, and social anhedonia and nicotine use, which is evident based on concurrent substance use data at both the baseline and 12-month time-points, and the potential significant difference in symptom severity between occasional and moderate smokers in experience of emotions and self found at baseline. The apparent strengthening of the inverse relationship between social anhedonia and nicotine use over time is intriguing. As this relationship was evident when examining 12-month nicotine use and symptom severity but not when examining the influence of baseline nicotine use on symptom severity over time, it is apparent that there is some change in nicotine use over time that is important in this relationship and that should be examined in future studies.

Consistent with previous reports, the current study did find an elevated rate of smoking among CHR participants as compared to healthy control participants, which suggests that alternative factors may be influencing smoking in the CHR individuals. The results of the current

study do not provide support for the self-medication hypothesis; future studies on this particular sample could investigate alternate aspects of the self-medication hypothesis. Additional research on other viable theories, particularly in regards to the potential neurobiological predisposition of psychotic and CHR individuals to nicotine addiction, should also be considered. As the results of the current study suggest that smoking behavior may be influenced by social behavior, further investigation into the relationship between early social connectedness and later substance use in CHR individuals should also be considered.

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Table 1

Medication, Substance Use, and Demographic Information by Diagnostic Group and Nicotine Use.

		Nicotine Use (cigarettes smoked)				
Diagnostic Group	Variable *n*(%)	None	Occasional	Moderate	Heavy	Test Statistics
Control (*n*=179)	**Age *m(SD)***	22.4(3.2)	24.1(4.0)	19.3(1.5)	24.8(4.1)	$F_3 = 3.23$, $p = 0.024$*
	Gender					
	Male	64(84.2)	8(10.5)	1(1.3)	3(3.9)	$\chi^2_3 = 2.89$, $p = 0.409$[a]
	Female	87(88.8)	7(7.1)	3(3.1)	1(1.0)	
	Other Substance Use					
	Marijuana Users	15(71.4)	3(14.3)	3(14.3)	0(0.0)	$\chi^2_3 = 10.92$, $p = 0.001$*[a]
	Alcohol Users	104(83.9)	14(11.3)	3(2.4)	3(2.4)	$\chi^2_3 = 7.76$, $p = 0.051$[a]
	Medication					
	Antipsychotic	0(0.0)	0(0.0)	0(0.0)	0(0.0)	$\chi^2_3 = 0.95$, $p = 0.816$[a]
	Antidepressant	2(100.0)	0(0.0)	0(0.0)	0(0.0)	$\chi^2_6 = 1.50$, $p = 0.959$[a]
	Stimulant	1(100.0)	0(0.0)	0(0.0)	0(0.0)	$\chi^2_6 = 1.22$, $p = 0.976$[a]
	Anticonvulsant	0(0.0)	0(0.0)	1(100.0)	0(0.0)	$\chi^2_6 = 8.68$, $p = 0.192$[a]
CHR (*n*=390)	**Age *m(SD)***	21.9(3.7)	20.9(2.9)	21.3(3.1)	22.0(3.5)	$F_3 = 1.22$, $p = 0.301$[b]
	Gender					
	Male	142(62.6)	31(13.7)	33(14.5)	21(9.3)	$\chi^2_3 = 8.18$, $p = 0.042$*
	Female	111(75.5)	9(6.1)	16(10.9)	11(7.5)	
	Other Substance Use					
	Marijuana Users	45 (44.6)	21(20.8)	21(20.8)	14(13.9)	$\chi^2_3 = 40.35$, $p = 0.000$*
	Alcohol Users	123(58.2)	29(13.7)	36(17.1)	23(10.9)	$\chi^2_3 = 20.89$, $p = 0.000$*
	Medication					
	Antipsychotic	31(66.0)	5(10.6)	7(14.9)	4(8.5)	$\chi^2_6 = 2.75$, $p = 0.840$[a]
	Antidepressant	63(71.6)	12(13.6)	8(9.1)	5(5.7)	$\chi^2_6 = 6.49$, $p = 0.370$[a]
	Stimulant	14(58.3)	4(16.7)	4(16.7)	2(8.3)	$\chi^2_6 = 7.80$, $p = 0.253$[a]
	Anticonvulsant	26(78.8)	2(6.1)	2(6.1)	3(9.1)	$\chi^2_6 = 5.83$, $p = 0.442$[a]

[a] Likelihood ratio reported because some cells have an expected count of less than five.
[b] Equal variances not assumed due to significant Levene's test of homogeneity of variances.
* Indicates significance at $p < .05$

Table 2

Spearman Correlations of Alcohol and Marijuana frequency variables with Nicotine Group.

Diagnostic Group	Variable	r_s	Significance
Control	Alcohol	0.253	p =0.001**
	Marijuana	0.169	p = 0.026*
CHR	Alcohol	0.274	p = 0.000**
	Marijuana	0.321	p = 0.000**

Note. Alcohol and Marijuana use here is measured on a five-point scale.
* Indicates significance at $p < .05$.
** Indicates significance at $p < .01$.

Table 3

Ordinal regression analysis on mean negative symptom score at baseline with nicotine group as the predictor variable and alcohol, marijuana, and sex included as covariates. Nicotine group comparison indicates the odds of the first group having a higher mean negative symptom compared to the second group.

Variable	Wald χ^2	β^b	95% CI	Significance
Comparison				
0 x 3	2.28	0.59	0.30-1.17	$p = 0.13$
1 x 0	0.50	0.80	0.43-1.49	$p = 0.48$
1 x 2	0.13	0.87	0.41-1.87	$p = 0.72$
1 x 3	3.02	0.47	0.20-1.10	$p = 0.08$
2 x 0	0.08	0.92	0.51-1.64	$p = 0.77$
2 x 3	2.21	0.54	0.24-1.22	$p = 0.14$
Covariates				
Alcohol	5.64	0.85	0.74-0.97	$p = 0.02$*
Marijuana	0.13	1.02	0.90-1.17	$p = 0.72$
Sex	3.50	1.45	0.98-2.13	$p = 0.06$

Note. Nicotine groups are coded as follows: "0" = No smoking, "1" = Occasional smoking, "2" = moderate smoking, "3" = heavy smoking. Odds ratio for "Sex" indicates odds of males having a higher mean score as opposed to females.

* Indicates significance at $p < .05$.

Table 4

Ordinal regression analyses on nicotine category and negative symptom scores at baseline.

Symptom	Comparison	Wald χ^2	β^b	95% CI	Significance
Social Anhedonia	0 x 3	0.64	1.31	0.67-2.56	$p = 0.34$
	1 x 0	0.61	0.78	0.43-1.45	$p = 0.44$
	1 x 2	0.92	1.44	0.68-3.04	$p = 0.34$
	1 x 3	0.01	1.03	0.45-2.35	$p = 0.42$
	2 x 0	4.37	0.54	0.31-0.96	$p = 0.04$*
	2 x 3	0.70	0.76	0.33-1.57	$p = 0.40$
Avolition	0 x 3	3.20	0.54	0.28-1.06	$p = 0.07$
	1 x 0	0.09	0.91	0.49-1.68	$p = 0.76$
	1 x 2	0.86	0.70	0.33-1.48	$p = 0.36$
	1 x 3	2.78	0.49	0.22-1.13	$p = 0.10$
	2 x 0	0.79	1.29	0.73-2.29	$p = 0.38$
	2 x 3	0.77	0.70	0.32-1.55	$p = 0.38$
Expression of Emotion	0 x 3	0.00	1.00	0.50-1.99	$p = 1.00$
	1 x 0	0.34	1.20	0.65-2.25	$p = 0.56$
	1 x 2	1.63	1.66	0.76-3.58	$p = 0.20$
	1 x 3	0.19	1.20	0.52-2.80	$p = 0.67$
	2 x 0	1.09	0.73	0.40-1.32	$p = 0.30$
	2 x 3	0.58	0.73	0.32-1.65	$p = 0.45$
Experience of Emotions and Self[a]	0 x 3	0.55	0.78	0.40-1.52	$p = 0.46$
	1 x 0	1.44	1.46	0.79-2.70	$p = 0.23$
	1 x 2	3.86	2.14	1.00-4.57	$p = 0.05$
	1 x 3	0.09	1.13	0.49-2.60	$p = 0.77$
	2 x 0	1.66	0.68	0.38-1.22	$p = 0.20$
	2 x 3	2.43	0.53	0.24-1.18	$p = 0.12$
Ideational Richness	0 x 3	0.46	0.78	0.39-1.59	$p = 0.50$
	1 x 0	0.01	1.04	0.54-2.00	$p = 0.91$
	1 x 2	0.13	0.87	0.39-1.92	$p = 0.72$
	1 x 3	0.21	0.81	0.34-1.95	$p = 0.64$
	2 x 0	0.35	1.20	0.65-2.21	$p = 0.55$
	2 x 3	0.02	0.94	0.41-2.17	$p = 0.89$
Occupational Functioning	0 x 3	4.39	0.49	0.25-0.96	$p = 0.04$*
	1 x 0	1.20	0.71	0.39-1.31	$p = 0.27$
	1 x 2	6.33	0.38	0.18-0.81	$p = 0.01$*
	1 x 3	6.23	0.35	0.15-0.80	$p = 0.01$*
	2 x 0	4.54	1.85	1.05-3.27	$p = 0.03$*
	2 x 3	0.06	0.91	0.41-1.99	$p = 0.81$

Note. Nicotine is coded: "0" = None, "1" = Occasional, "2" = Moderate, "3" = Heavy.
[a] Test of parallel lines was significant for this analysis.
* Indicates significance at $p < .05$.

Table 5

Ordinal regression coefficients for substance and gender covariates at baseline.

Symptom	Covariate	Wald χ^2	β^b	95% CI	Significance
Social Anhedonia	Alcohol	6.76	0.84	0.73-0.96	$p = 0.01$*
	Marijuana	0.00	1.00	0.88-1.14	$p = 1.00$
	Sex	0.54	0.87	0.60-1.27	$p = 0.46$
Avolition	Alcohol	0.42	0.96	0.84-1.09	$p = 0.52$
	Marijuana	0.28	1.04	0.91-1.18	$p = 0.60$
	Sex	0.55	1.15	0.79-1.68	$p = 0.46$
Expression of Emotion	Alcohol	0.02	1.00	0.87-1.15	$p = 0.97$
	Marijuana	0.74	0.94	0.82-1.08	$p = 0.40$
	Sex	5.65	1.61	1.09-2.38	$p = 0.02$*
Experience of Emotions and Self[a]	Alcohol	0.88	1.07	0.93-1.22	$p = 0.35$
	Marijuana	0.75	0.94	0.83-1.08	$p = 0.39$
	Sex	0.00	1.01	0.69-1.47	$p = 0.97$
Ideational Richness	Alcohol	5.50	0.84	0.73-0.97	$p = 0.02$*
	Marijuana	0.30	0.96	0.84-1.11	$p = 0.59$
	Sex	6.72	1.71	1.14-2.58	$p = 0.01$*
Occupational Functioning	Alcohol	9.06	0.81	0.71-0.93	$p = 0.00$*
	Marijuana	0.10	1.02	0.90-1.16	$p = 0.76$
	Sex	2.30	1.39	0.96-2.03	$p = 0.08$

Note. Odds ratios presented for "Sex" indicate the odds of having a higher negative symptom score for males versus females.

[a] Test of parallel lines was significant for this analysis.

* Indicates significance at $p < .05$.

Table 6

Ordinal regression analysis on mean negative symptom score at the 12-Month follow-up visit with nicotine group as the predictor variable and alcohol, marijuana, and sex included as covariates. Nicotine group comparison indicates the odds of the first group having a higher mean negative symptom compared to the second group.

Variable	Wald χ^2	β^b	95% CI	Significance
Comparison				
0 x 3	0.02	1.09	0.31-3.85	$p = 0.90$
1 x 0	0.01	1.04	0.45-2.38	$p = 0.93$
1 x 2	1.40	1.88	0.66-5.33	$p = 0.24$
1 x 3	0.03	1.13	0.27-4.67	$p = 0.87$
2 x 0	2.17	0.55	0.25-1.22	$p = 0.14$
2 x 3	0.52	0.60	0.15-2.42	$p = 0.47$
Covariates				
Alcohol	3.61	0.84	0.70-1.01	$p = 0.06$
Marijuana	0.01	1.01	0.85-1.19	$p = 0.93$
Sex	1.43	1.38	0.82-2.33	$p = 0.23$

Note. Nicotine is coded: "0" = None, "1" = Occasional, "2" = Moderate "3" = Heavy. Odds ratio for "Sex" indicates odds of males having a higher mean score as opposed to females.
* Indicates significance at $p < .05$.

Table 7

Ordinal regression analyses on nicotine category and negative symptom scores at 12-Months.

Symptom	Comparison	Wald χ^2	β^b	95% CI	Significance
Social Anhedonia	0 x 3	0.37	1.47	0.43-5.07	$p = 0.54$
	1 x 0	1.82	0.57	0.25-1.29	$p = 0.18$
	1 x 2	3.61	2.77	0.97-7.91	$p = 0.06$
	1 x 3	0.06	0.84	0.21-3.37	$p = 0.80$
	2 x 0	14.42	0.21	0.09-0.47	$p = 0.00$*
	2 x 3	2.86	0.30	0.08-1.21	$p = 0.09$
Avolition[a]	0 x 3	0.00	1.01	0.29-3.53	$p = 0.98$
	1 x 0	0.30	1.25	0.56-2.83	$p = 0.59$
	1 x 2	0.51	1.45	0.52-4.01	$p = 0.48$
	1 x 3	0.11	1.27	0.31-5.15	$p = 0.74$
	2 x 0	0.14	0.87	0.40-1.87	$p = 0.71$
	2 x 3	0.04	0.88	0.22-3.46	$p = 0.85$
Expression of Emotion	0 x 3	0.16	0.78	0.22-2.74	$p = 0.69$
	1 x 0	0.67	0.69	0.28-1.68	$p = 0.42$
	1 x 2	0.00	1.04	0.34-3.15	$p = 0.95$
	1 x 3	0.72	0.54	0.13-2.28	$p = 0.40$
	2 x 0	0.91	0.67	0.29-1.53	$p = 0.34$
	2 x 3	0.84	0.52	0.13-2.12	$p = 0.36$
Experience of Emotions and Self	0 x 3	0.73	0.58	0.17-2.01	$p = 0.39$
	1 x 0	0.06	1.11	0.49-2.56	$p = 0.80$
	1 x 2	0.37	1.38	0.49-3.92	$p = 0.55$
	1 x 3	0.37	0.65	0.16-2.62	$p = 0.54$
	2 x 0	0.28	0.81	0.37-1.78	$p = 0.60$
	2 x 3	1.16	0.47	0.12-1.85	$p = 0.28$
Ideational Richness	0 x 3	1.37	0.46	0.13-1.68	$p = 0.24$
	1 x 0	0.28	1.23	0.53-3.05	$p = 0.60$
	1 x 2	0.83	1.69	0.55-5.24	$p = 0.36$
	1 x 3	0.52	0.59	0.14-2.51	$p = 0.47$
	2 x 0	0.43	0.75	0.31-1.79	$p = 0.51$
	2 x 3	2.05	0.35	0.08-1.48	$p = 0.15$
Occupational Functioning	0 x 3	0.73	0.58	0.17-2.02	$p = 0.39$
	1 x 0	1.65	1.71	0.75-3.86	$p = 0.20$
	1 x 2	0.47	1.43	0.52-3.95	$p = 0.49$
	1 x 3	0.00	0.99	0.25-3.99	$p = 0.99$
	2 x 0	0.21	1.20	0.55-2.58	$p = 0.65$
	2 x 3	0.27	0.70	0.18-2.72	$p = 0.60$

Note. Nicotine groups are coded: "0" = None, "1" = Occasional, "2" = Moderate, "3" = Heavy.
[a] Test of parallel lines was significant for this analysis.
* Indicates significance at $p < .05$.

Table 8

Ordinal regression coefficients for substance and gender covariates at the 12-Month follow-up visit.

Symptom	Covariate	Wald χ^2	β^b	95% CI	Significance
Social Anhedonia	Alcohol	6.83	0.79	0.66-0.94	$p = 0.01$*
	Marijuana	1.15	0.91	0.77-1.08	$p = 0.28$
	Sex	1.67	1.41	0.84-2.35	$p = 0.20$
Avolition[a]	Alcohol	0.33	0.95	0.80-1.13	$p = 0.57$
	Marijuana	0.23	0.96	0.81-1.14	$p = 0.63$
	Sex	0.40	1.18	0.71-1.98	$p = 0.53$
Expression of Emotion	Alcohol	0.64	0.93	0.77-1.12	$p = 0.42$
	Marijuana	0.26	1.05	0.88-1.25	$p = 0.61$
	Sex	5.34	1.94	1.11-3.39	$p = 0.02$*
Experience of Emotions and Self	Alcohol	0.05	1.02	0.86-1.22	$p = 0.82$
	Marijuana	0.91	1.09	0.92-1.28	$p = 0.34$
	Sex	0.74	1.26	0.74-2.15	$p = 0.39$
Ideational Richness	Alcohol	7.12	0.76	0.63-0.93	$p = 0.01$*
	Marijuana	0.19	1.04	0.87-1.25	$p = 0.67$
	Sex	2.55	1.59	0.90-2.82	$p = 0.11$
Occupational Functioning	Alcohol	1.61	0.81	0.71-0.93	$p = 0.20$
	Marijuana	2.70	1.02	0.90-1.16	$p = 0.10$
	Sex	3.24	1.39	0.96-2.03	$p = 0.07$

Note. Odds ratios presented for "Sex" indicate the odds of having a higher negative symptom score for males versus females.

[a] Test of parallel lines was significant for this analysis.

* Indicates significance at $p < .05$.

Table 9

Repeated Measures ANCOVA coefficients for within-subjects factors based on nicotine and covariates. The within-subjects factor used baseline symptom score and 12-month symptom score. All substance use variables are from the baseline time-point.

Symptom	Variable	*SS*	*df*	*MS*	*F*	*Signif.*
Mean Overall Score	Nicotine	1.40	3	0.47	0.90	0.44
	Alcohol	1.20	1	1.20	2.32	0.13
	Marijuana	0.39	1	0.39	0.74	0.39
	Sex	0.76	1	0.76	1.47	0.23
Social Anhedonia	Nicotine	2.82	3	0.94	0.84	0.48
	Alcohol	1.49	1	1.49	1.32	0.25
	Marijuana	2.23	1	2.23	1.98	0.16
	Sex	6.41	1	6.41	5.70	0.02*
Avolition	Nicotine	5.66	3	1.89	1.33	0.26
	Alcohol	0.24	1	0.24	0.17	0.68
	Marijuana	0.48	1	0.48	0.34	0.56
	Sex	0.99	1	0.99	0.70	0.40
Expression of Emotion	Nicotine	3.31	3	1.10	1.37	0.26
	Alcohol	0.01	1	0.01	0.01	0.91
	Marijuana	0.00	1	0.00	0.00	0.99
	Sex	0.25	1	0.25	0.30	0.58
Experience of Emotions and Self	Nicotine	2.57	3	0.86	0.56	0.65
	Alcohol	2.14	1	2.14	1.39	0.24
	Marijuana	0.61	1	0.61	0.39	0.53
	Sex	2.82	1	2.82	1.83	0.18
Ideational Richness	Nicotine	0.18	3	0.06	0.11	0.96
	Alcohol	0.59	1	0.59	1.06	0.31
	Marijuana	0.21	1	0.21	0.38	0.54
	Sex	0.01	1	0.01	0.01	0.92
Occupational Functioning	Nicotine	8.18	3	2.73	0.96	0.41
	Alcohol	1.60	1	1.60	0.56	0.46
	Marijuana	2.07	1	2.07	0.73	0.40
	Sex	3.10	1	3.10	1.09	0.30

Note. SS = Sum of Squares; MS = Mean Square
* Indicates significance at $p < .05$.

Table 10

Ordinal regression analysis on mean negative symptom score at baseline with the nicotine group and sex interaction variable.

Comparison	Wald χ^2	β^b	95% CI	Significance
0 x 3	0.50	1.65	0.41-6.65	$p = 0.48$
1 x 0	5.01	0.20	0.05-0.82	$p = 0.03$*
1 x 2	3.47	0.19	0.03-1.09	$p = 0.06$
1 x 3	1.38	0.32	0.05-2.13	$p = 0.24$
2 x 0	0.00	1.03	0.32-3.36	$p = 0.96$
2 x 3	0.37	1.70	0.31-9.39	$p = 0.54$

Note. Interactions are coded: ("0" = None, "1" = Occasional, "2" = Moderate, "3" = Heavy).
[a] Test of parallel lines was significant for this analysis.
* Indicates significance at $p < 0.05$.

Table 11

Ordinal regression analyses with sex and nicotine interaction at baseline.

Symptom	Comparison	Wald χ^2	β^b	95% CI	Significance
Social Anhedonia	0 x 3	0.13	1.29	0.33-5.03	$p = 0.72$
	1 x 0	4.23	0.23	0.06-0.94	$p = 0.04$*
	1 x 2	3.67	0.19	0.03-1.04	$p = 0.06$
	1 x 3	1.65	0.30	0.05-1.89	$p = 0.20$
	2 x 0	0.12	0.21	0.39-3.92	$p = 0.73$
	2 x 3	0.29	1.59	0.30-8.44	$p = 0.59$
Avolition[a]	0 x 3	0.03	0.89	0.23-3.48	$p = 0.87$
	1 x 0	0.31	2.15	0.08-1.24	$p = 0.10$
	1 x 2	1.41	0.36	0.07-1.96	$p = 0.24$
	1 x 3	0.11	0.27	0.04-1.74	$p = 0.17$
	2 x 0	0.87	1.41	0.27-2.75	$p = 0.81$
	2 x 3	0.04	0.77	0.15-4.10	$p = 0.76$
Expression of Emotion	0 x 3	0.98	2.03	0.50-8.18	$p = 0.32$
	1 x 0	0.05	0.85	0.20-3.55	$p = 0.83$
	1 x 2	0.00	1.01	0.17-5.92	$p = 1.00$
	1 x 3	0.32	1.72	0.26-11.4	$p = 0.57$
	2 x 0	0.07	0.85	0.25-2.89	$p = 0.79$
	2 x 3	0.37	1.72	0.30-9.75	$p = 0.54$
Experience of Emotions and Self	0 x 3	0.64	1.75	0.45-6.87	$p = 0.42$
	1 x 0	2.23	0.34	0.09-1.40	$p = 0.14$
	1 x 2	4.44	0.15	0.03-0.88	$p = 0.04$*
	1 x 3	0.29	0.60	0.09-3.83	$p = 0.59$
	2 x 0	1.73	2.25	0.67-7.50	$p = 0.19$
	2 x 3	2.46	3.93	0.71-21.7	$p = 0.12$
Ideational Richness[a]	0 x 3	0.04	0.86	0.20-3.75	$p = 0.84$
	1 x 0	0.39	0.62	0.14-2.76	$p = 0.53$
	1 x 2	0.04	1.17	0.24-5.64	$p = 0.85$
	1 x 3	0.38	0.54	0.07-3.90	$p = 0.54$
	2 x 0	0.02	0.93	0.26-3.24	$p = 0.90$
	2 x 3	0.06	0.80	0.13-4.87	$p = 0.80$
Occupational Functioning[a]	0 x 3	0.07	0.84	0.22-3.26	$p = 0.80$
	1 x 0	1.48	0.42	0.11-1.70	$p = 0.22$
	1 x 2	1.58	0.34	0.06-1.84	$p = 0.21$
	1 x 3	1.23	0.35	0.06-2.24	$p = 0.27$
	2 x 0	0.15	1.26	0.40-3.97	$p = 0.70$
	2 x 3	0.00	1.05	0.20-5.56	$p = 0.95$

Note. Interactions are coded: ("0" = None, "1" = Occasional, "2" = Moderate, "3" = Heavy).
[a] Test of parallel lines was significant for these analyses.
* Indicates significance at $p < 0.05$.

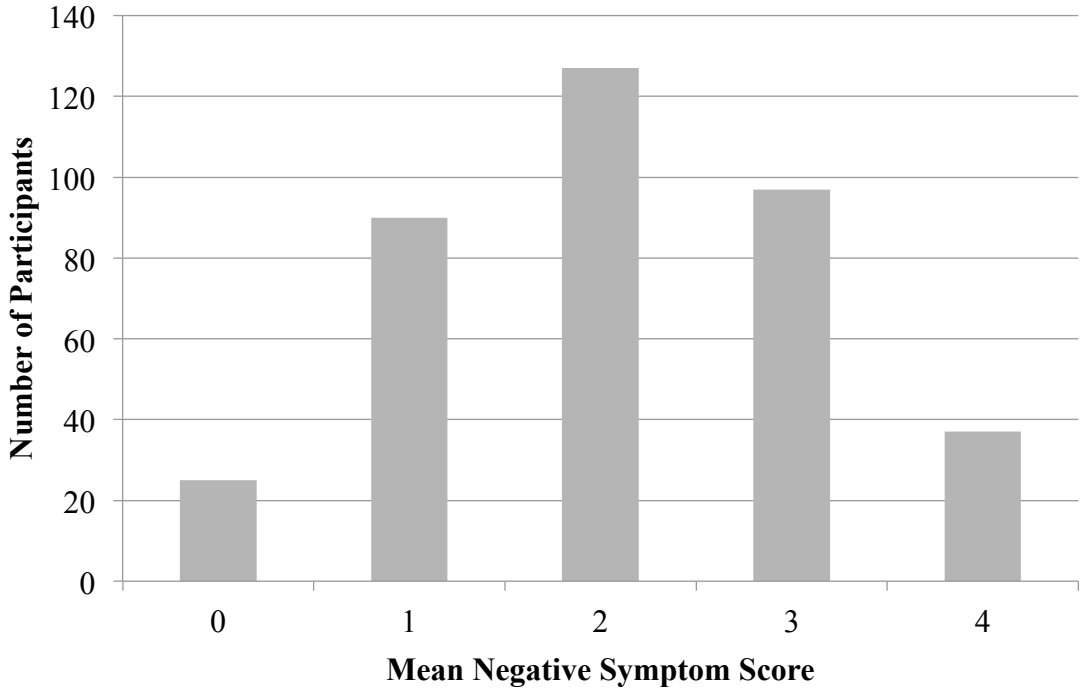

Figure 1. Mean negative symptom scores at baseline of participants in the Clinical High-Risk (CHR) group. Mean score was calculated by averaging the score of the six individual negative symptoms.

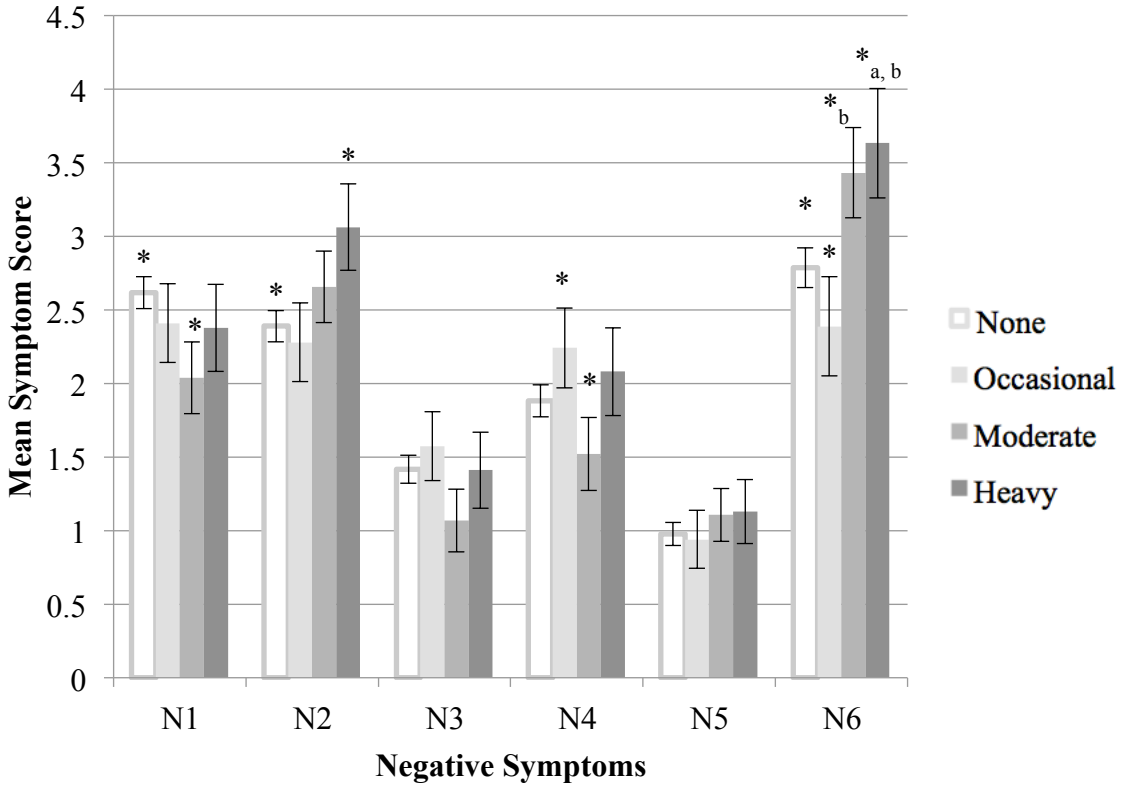

Figure 2. Mean negative symptom scores at baseline for members of the Clinical High-Risk (CHR) group based on Nicotine group. Higher scores indicate more severe symptoms. Symptoms are coded as follows: Social Anhedonia (N1), Avolition (N2), Expression of Emotion (N3), Experience of Emotions and Self (N4), Ideational Richness (N5), and Occupational Functioning (N6). Error bars indicate the standard error of the mean.
* Indicates significant difference between means at $p < 0.05$.
[a] This group significantly differ from the "None" group.
[b] These groups significantly differ from the "Occasional" group.

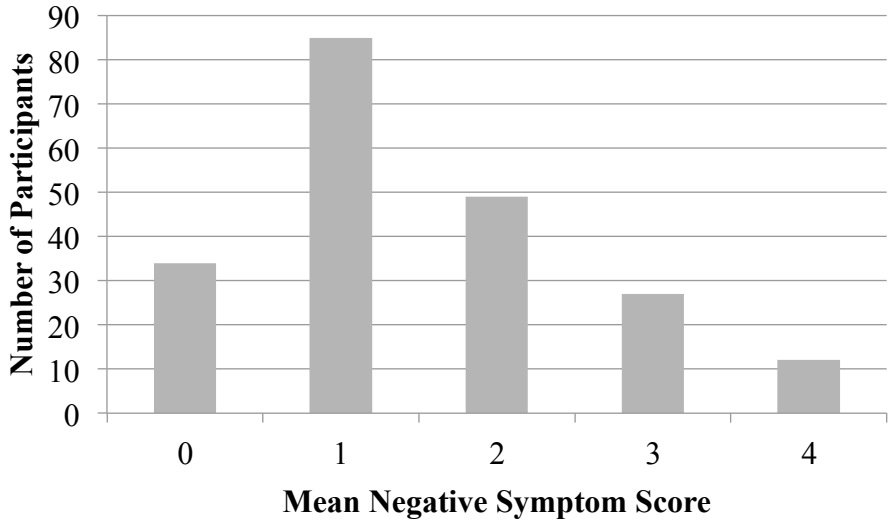

Figure 3. Mean negative symptom score of participants at the 12-month follow-up visit in the Clinical High-Risk (CHR) group. Mean score was calculated by averaging the score of the six individual negative symptoms.

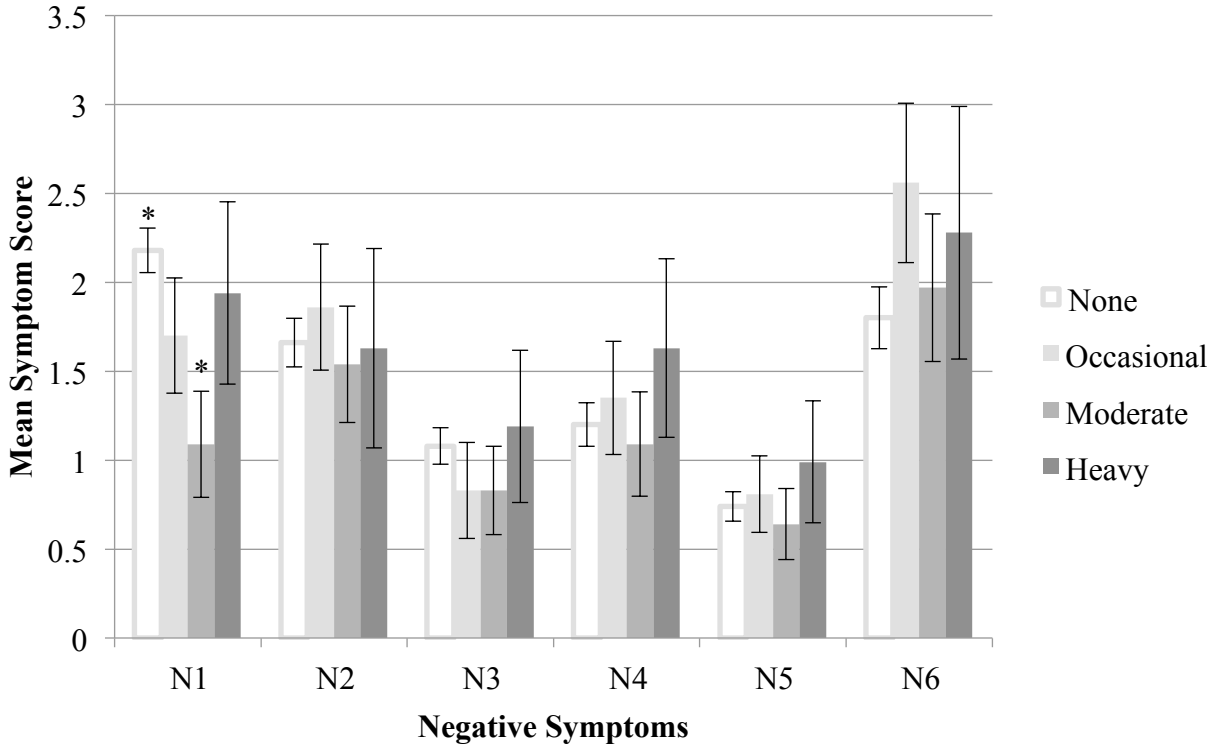

Figure 4. Mean negative symptom scores for members of the Clinical High-Risk (CHR) group based on Nicotine group at 12 Months. Higher scores indicate more severe symptoms. Symptoms are coded as follows: Social Anhedonia (N1), Avolition (N2), Expression of Emotion (N3), Experience of Emotions and Self (N4), Ideational Richness (N5), and Occupational Functioning (N6). Error bars indicate the standard error of the mean.
* Indicates significant difference between means at $p < .05$.

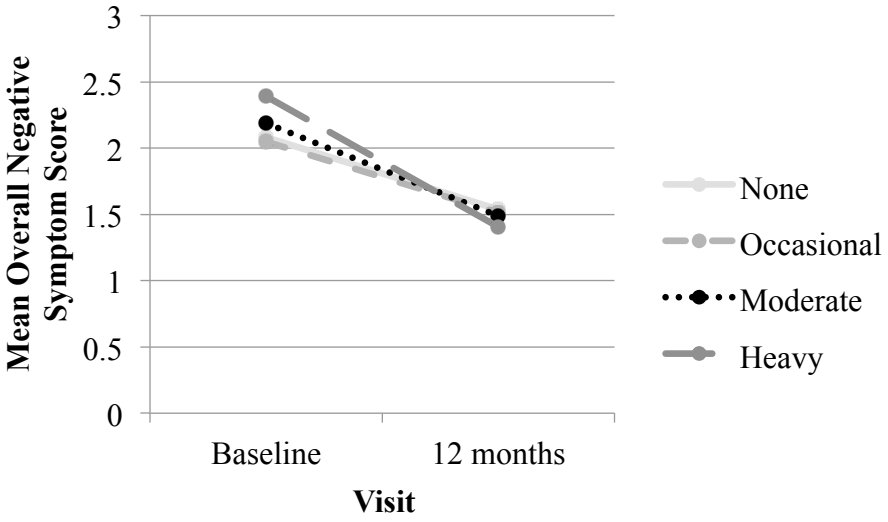

Figure 5. Mean Overall Negative symptom scores at Baseline and 12 months by baseline nicotine use. A higher score indicates more severe overall negative symptoms. Please see Table 9 for the test statistics produced from this analysis.

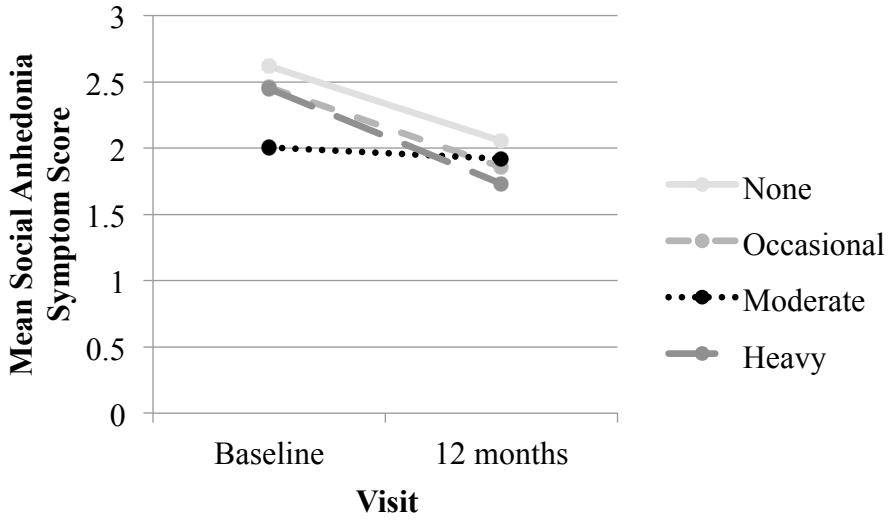

Figure 6. Mean Social Anhedonia (N1) symptom scores at Baseline and 12 months by baseline nicotine use. A higher score indicates a more severe symptom (e.g., higher levels of social anhedonia). Please see Table 9 for the test statistics produced from this analysis.

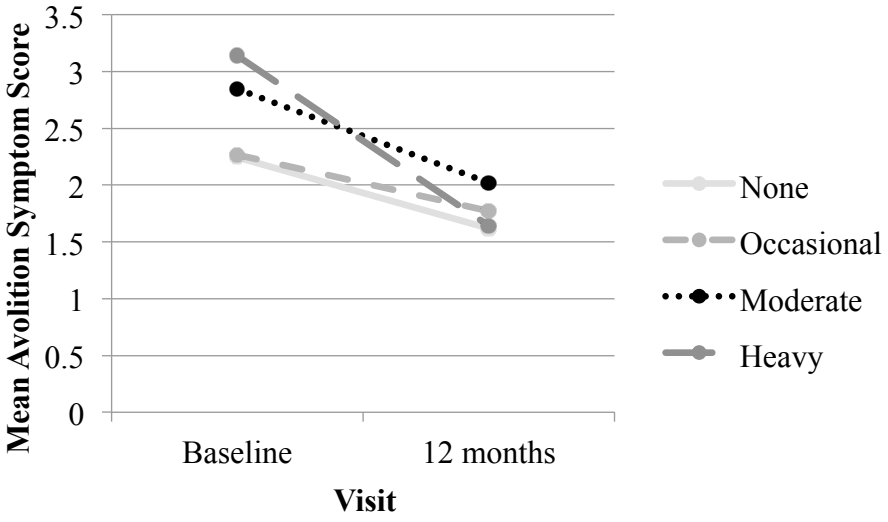

Figure 7. Mean Avolition (N2) symptom scores at Baseline and 12 months by baseline nicotine use. A higher score indicates a more severe symptom (e.g., higher levels of avolition). Please see Table 9 for the test statistics produced from this analysis.

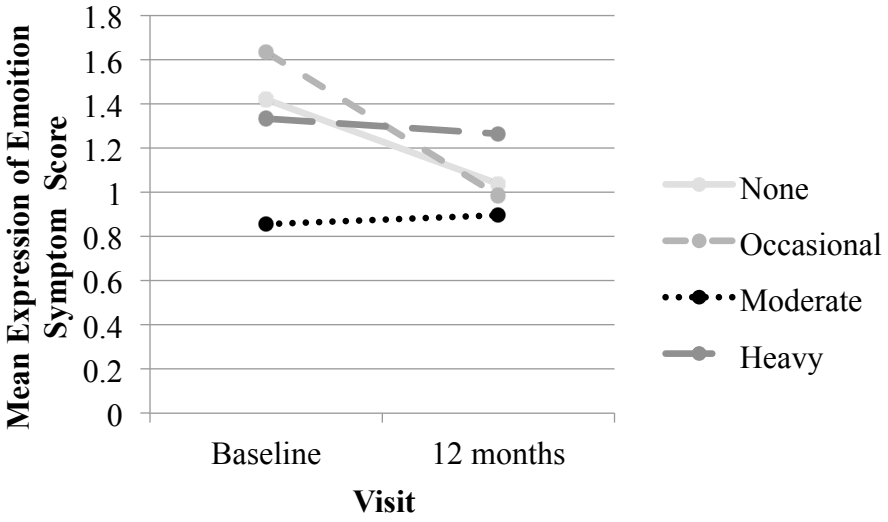

Figure 8. Mean Expression of Emotion (N3) symptom scores at Baseline and 12 months by baseline nicotine use. A higher score indicates more severe impairment (e.g., decreased expression of emotion). Please see Table 9 for the test statistics produced from this analysis.

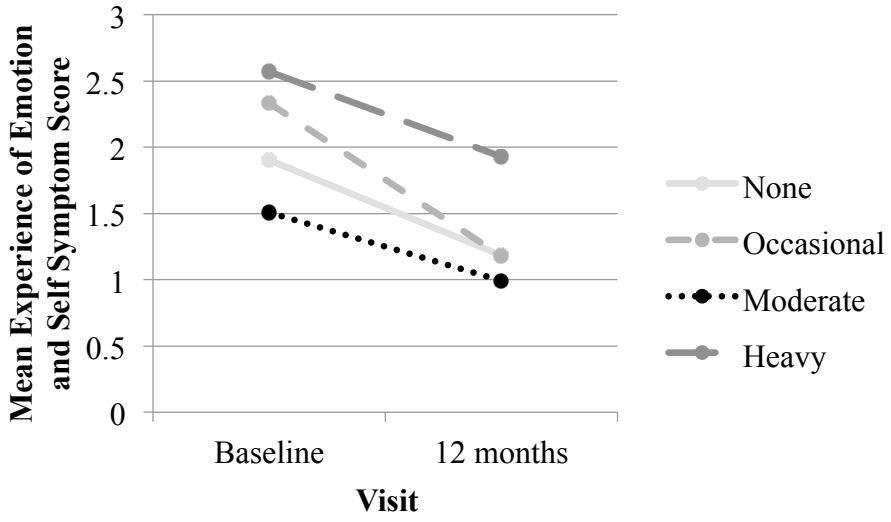

Figure 9. Mean Experience of Emotion and Self (N4) symptom scores at Baseline and 12 months by baseline nicotine use. A higher score indicates more severe impairment (e.g., decreased experience of emotion and self). Please see Table 9 for the test statistics produced from this analysis.

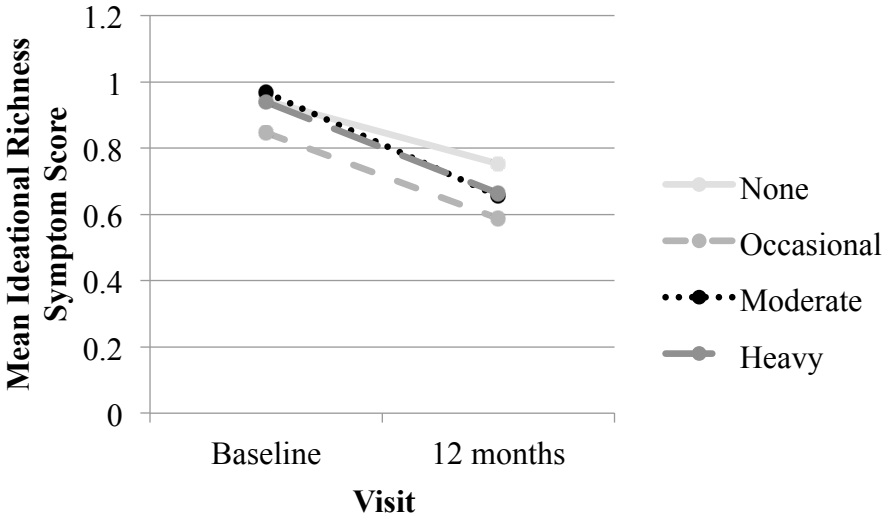

Figure 10. Mean Ideational Richness (N5) symptom scores at Baseline and 12 months by baseline nicotine use. A higher score indicates more severe impairment (e.g., decreased ideational richness). Please see Table 9 for the test statistics produced from this analysis.

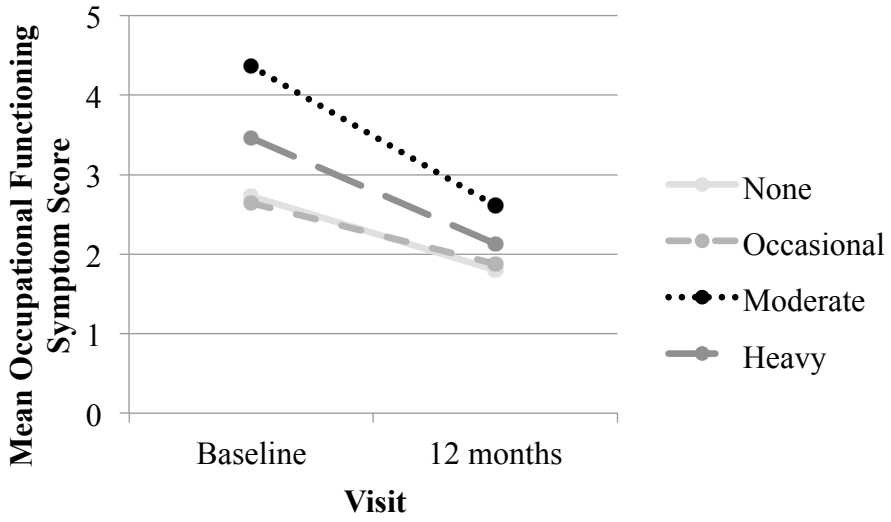

Figure 11. Mean Occupational Functioning (N6) symptom scores at Baseline and 12 months by baseline nicotine use. A higher score indicates more severe impairment (e.g., more impaired occupational functioning). Please see Table 9 for the test statistics produced from this analysis.