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Abstract

Tobacco dependence in patients with schizophrenia is an increasing concern with few treatment options. Individuals with Schizophrenia have a cigarette smoking prevalence rate which is significantly higher than the general population. Consequently, patients also have a lower quit rate than the general population. The increased prevalence of tobacco use in this population complicates symptoms and also has adverse physiological effects on patients. Recent studies have demonstrated that patients with schizophrenia smoke before the onset of the illness and also start smoking earlier than the average population. Patients also become psychotic earlier than patients who do not smoke, and also require higher doses of anti-psychotic medications. This review examines recent literature and discusses models proposed to explain the relationship between tobacco dependence and schizophrenia and concludes by discussing treatment options for smokers with schizophrenia.

Introduction

Tobacco addiction is the most common occurring disorder in the serious mental illness (SMI) population (Ziedonis et al. 2003). About 75-85% of individuals with schizophrenia, bipolar disorder and other SMI use tobacco (Ziedonis et al. 2003). Tobacco use not only reduces quality of life in these patients, but also leads to death caused by medical diseases (Ziedonis et al. 2003). Among the serious mental illness (SMI) population, individuals with Schizophrenia have the highest prevalence of tobacco dependence (Etter, 2004). Schizophrenia is one of the most debilitating mental illnesses, affecting approximately 1% of the global population (Schultz et al. 2007). The illness is characterized by profound disruption in cognition and emotion, affecting fundamental human attributes such as language, thought, perception, affect, and sense of self. The array of symptoms frequently includes psychotic manifestations, such as hearing internal voices or experiencing other sensations not connected to an obvious source (hallucinations) and assigning unusual significance or meaning to normal events or holding fixed false personal beliefs (delusions). According to the DSM-IV manual for diagnosing psychosis, no single symptom is definitive for diagnosis. Instead, the diagnosis is made using a pattern of signs and symptoms, in conjunction with impaired occupational or social functioning and duration of these characteristics. (DSM-IV). Tobacco dependence is a growing concern in this population. Individuals with schizophrenia have a two to four times higher rate of tobacco dependence than the general population as well (Schultz et al. 2007). Additionally, patients smoke more heavily and have lower quit rates than the general population (Patkar et al. 2002). Moreover,

studies have shown that patients with schizophrenia in the United States alone smoke about \$20 billion worth of cigarettes every year (Patkar et al. 2002). This is a high economic burden to patients and society that makes cigarette smoking in this population a greater concern.

Individuals with schizophrenia smoke an average of 25 cigarettes per day (Williams et al. 2005). This is significantly higher than that of the general population (Williams et al. 2005). The harmful effects of cigarette smoking among schizophrenia patients include high rates of cancer, cardiovascular and respiratory diseases, and increased psychiatric symptoms (Ziedonis et al. 2003). Also, tobacco dependence in this population may prompt alcohol and drug craving which increases the risk for a substance relapse (Ziedonis et al. 2003). As a result of these harmful effects of tobacco dependence, it is necessary to assess the reason why patients with schizophrenia have high rates of tobacco dependence. Understanding the cause and effect models may help in developing more effective smoking cessation treatment options for this population.

Demographics and clinical symptoms

The onset of schizophrenia is usually seen during the teenage years or early 20s in men whereas the onset in women the onset is usually seen in their late 20s or early 30s (Schultz et al. 2007). Although the incidence of the illness is slightly higher among men, women are just as likely to develop the disease (Hays 2000). In both genders, the onset of the illness is preceded by a premonitory phase, which typically occurs during childhood (Tandon et al. 2009). This phase is characterized by mild cognitive, motor or social deficits and

sometimes presents depression like symptoms (Tandon et al. 2009). Although the next phase may vary in the time of occurrence, the prodromal phase of the illness usually begins to appear during adolescence (Tandon et al. 2009). This phase is characterized by functional deficits and very brief positive symptoms (Tandon et al. 2009). The positive symptoms of schizophrenia are reality-distorting symptoms that include delusions and hallucinations and can be of auditory or visual nature that begin to get florid during the psychotic stage that follows the prodromal phase (Tandon et al. 2009). The psychotic stage is then followed by a stable stage that is characterized by social and functional decline, cognitive difficulties and negative symptoms (Tandon et al. 2009). The negative symptoms include a loss of affective functions such as social withdrawal, loss of motivation, poverty of speech, lack of interest, pleasure and initiative (Table 1). Negative

Positive Symptoms	Negative symptoms
Delirium	Loss of affect
Auditory or visual hallucinations	Social withdrawal
Auditory or visual delusions	Loss of mood
Psychosis	Poor speech
	Lack of interest, pleasure and initiative
	Poor hygiene

Table 1. Symptoms of Schizophrenia. Source: Tandon R, Nasrallah HA, & MS., K. (2009). Schizophrenia, "just the facts" 4. clinical features and conceptualization. Schizophrenia Research.

symptoms can also cause more functional disruption than psychoses. Other clinical symptoms of schizophrenia include anxiety, impaired insight, disorientation of thought and behavior, sensory and motor impairments and mood disorders (Tandon et al. 2009). Individuals with schizophrenia also have high mortality rates. They are more prone to attempt suicide because of poor lifestyle and have more medical illnesses as well (Tandon et al. 2009).

Risk Factors

Although the exact cause of schizophrenia is still unknown, genetic, biological, environmental and neurodevelopment risks have been proposed to explain schizophrenia. The following risk factors are discussed below: Genetic factors, environmental, elevated neurotransmitter theory

and neurodevelopment theory, and the substance use risk factor.

Genetic and family studies have shown that those with a parent or sibling, who have schizophrenia, are ten times more likely to develop the illness themselves and those with two affected parents are fifty times more likely to develop the illness (Freedman 2003).

Monozygotic twins and adopted children whose biological mothers have schizophrenia also show a greater risk of developing the illness themselves (Hays 2000).

One proposed theory about schizophrenia symptoms is that individuals with the illness tend to have elevated neurotransmitter dopamine levels in their brains. This theory is based on the effects of drugs (stimulants) that increased dopaminergic neurotransmission (Hays 2000). It was also found that when individuals with schizophrenia were treated with antipsychotic medication, there was a decrease in dopaminergic neurotransmission in the brain and patients displayed better functionality on perceptual levels and displayed less positive symptoms (Hays 2000).

The environmental factors that may cause the illness include the sensitivity of these individuals to their daily surroundings such as season, urbanization, socioeconomic status and familial relationships and an interaction of all these factors increase the incidence of the illness (Schultz et al. 2007).

The neurodevelopment hypothesis of schizophrenia is a major current theory that also proposes a risk factor for schizophrenia. This hypothesis proposes that abnormalities of early brain development that affect critical circuits in the brain can increase the subsequent risk of the clinical symptoms of schizophrenia. The hypothesis is derived from observations such as frequency of obstetrical complications, prenatal exposure to infectious agents or toxins, and subtle physical and neuropsychological impairments that contribute to brain abnormalities (Marenco and Weinberger 2000). It also posits that during the second trimester of development, the prenatal effects include deficits in the dorsolateral prefrontal cortex (DLPFC). This area later affects working memory tasks, which contribute to the symptoms of schizophrenia. However, the hypothesis is not conclusive because most patients do not begin to see signs of the illness until adolescence (Hyman 2001). This is because the myelination of the neurons in the DLPFC is a developmental process and it is the last area in the brain to begin myelination (Hyman 2001). Thus, any lesions or abnormalities in the brain that

occur during the prenatal period would not have a significant impact on behavior until early adulthood (Hyman 2001). Therefore, the neurodevelopment hypothesis is also likely to be a risk factor of schizophrenia as it is responsible for many cognitive deficits that are later seen in the illness.

Substance use as a risk factor

Schizophrenia is often triggered by the interaction of all the above-mentioned risk factors (Schultz et al. 2007). However, another major risk factor for individuals with schizophrenia is the use of illicit drugs alcohol and especially cigarette smoking. Schizophrenia patients have a two to four time's higher rate of cigarette smoking than the general population (Schultz et al. 2007). The risk of cigarette smoking has been of great concern in individuals with schizophrenia as recent research has demonstrated that not only do patients with schizophrenia smoke before the onset of their illness, they start smoking earlier than the average population and also become psychotic earlier than average schizophrenia patient who does not smoke. In addition, they also require more medication as tar in tobacco is known to increase the CYP1A2 isoenzyme activity (Hays 2000). This interferes with many psychiatric medications and reduces antipsychotic blood levels, which causes the patient to require higher doses of the medication (Hays 2000). As a result, since patients require double the medication, they also experience greater side effects (Ziedonis et al. 2003). Tobacco dependence in this population also leads to the high mortality rates seen in this population and those with substance abuse have their first hospitalization at earlier ages and are more frequently hospitalized thereafter.

Models that explain the relationship between cigarette smoking and Schizophrenia

Several models have been proposed to explain why individuals with schizophrenia tend to smoke more than the general population. Some of these models tend to explain the perceived benefits of cigarette smoking upon patients. Also these models explain why individuals with schizophrenia have a higher rate of cigarette smoking. But one must keep in mind that despite the apparent short-term benefits of cigarettes among this population, negative long-term consequences easily outweigh any of the benefits the patients receive from cigarette smoking as they do in all circumstances.

The first model is the "self-medication" model of negative symptoms, which states that individuals with schizophrenia use cigarettes as a way to ease their depressive and psychotic

symptoms (Patkar et al. 2002). Patients suffering from schizophrenia may use nicotine to self-medicate for several reasons. Firstly, nicotine is known to improve cognitive processes related to prefrontal functions such as attention or working memory. Nicotine acts as a facilitator in these processes by the modulation of the signal-to-noise ratio and synchrony of neuronal activity in the prefrontal cortex Secondly, nicotine may increase plastic processes in the hippocampus that are beneficial for cognitive deficits in schizophrenia related to learning and memory. Lastly, nicotine may improve symptoms related to mood and stress by modulation of the reward and stress response systems of the brain. (Mobascher & Winterer, 2008). The following studies support the self-medication model as well. A study conducted at an inpatient psychiatric hospital, reported significant positive correlations between the Fagerstrom Test for Nicotine Dependence (FTND) which measures severity of smoking, and the Positive and Negative syndrome Scale (PANSS) which provides an assessment of various negative symptoms. These significant findings that the severity of tobacco use was positively associated with negative symptoms, reflected difficulties in attention, orientation and thinking in individuals with schizophrenia (Patkar et al. 2002). This result was consistent with the fact that patients with greater negative symptoms may use smoking as "self-medication" to treat their impairments (Patkar et al. 2002). Since patients with major negative symptoms tend to avoid social interactions and other social activities because of their illness, a plausible reason to explain their tobacco dependence may also be that smoking may simply be a "time filler" and a way to avoid boredom for the patients (Patkar et al. 2002).

Another reason why individuals with schizophrenia have a high tobacco dependence rate is because they usually have great difficulties in quitting smoking (deLeon 1996). In a pilot study conducted with twenty-six individuals with chronic schizophrenia hospitalized in a research unit at State hospital, it was found that only 8% of the patients quit smoking (deLeon 1996). This is steady with the finding that since patients use tobacco as a "self-medication" to calm their negative symptoms, quitting can become a great challenge for many patients.

Individuals with schizophrenia are known to suffer from cognitive impairments. In a study conducted by T.J. Taiminen et al., forty-nine of the eighty-eight patients recruited were smokers. The main result of the study was that smokers with high scores on the five-factor PANSS model for

the symptoms of schizophrenia, which includes conceptual disorganization (P2), disorientation (G10), difficulty in abstract thinking (N5), mannerisms and posturing (G5), and poor attention (G11) were associated with heavy smoking (Tero et al. 1998). The high scores showed that smoking improved many aspects of patients' cognitive functioning by either adjusting abnormally low prefrontal dopamine activity or by enhancing the functioning of cholinergic pathways in the brain. A study conducted by Sacco et al assessed 25 smokers with schizophrenia and 25 control smokers (Sacco et al. 2005). After a series of neuropsychological assessments, it was found that cigarette smoking selectively enhances the visual spatial working memory and attention deficits in smokers with schizophrenia (Sacco et al. 2005). This also explains the high rate of tobacco dependence among individuals with schizophrenia because the working memory and attention play an immense role in cognitive behavior and if smoking is shown to facilitate that behavior then it acts as a way of self-medication for this population.

More studies have reported that the early symptoms of schizophrenia cause the initiation of smoking. It has been suggested that individuals with schizophrenia are motivated to smoke because smoking not only acts as a coping mechanism for this population but also provides temporary relief from psychiatric symptoms (Forchuk et al. 2002). The prodromal phase of schizophrenia takes place about one or two years before the onset of the psychotic symptoms of schizophrenia. During this phase patients usually experience symptoms of anxiety, poor attention, and social withdrawal (Ballas 2007). It is not until the late prodromal phase when the positive symptoms of the illness begin to appear (Ballas 2007). A study conducted from data collected from a Northern Finland birth cohort (n=11017) and through the National Finish Hospital Discharge Registry it was found that 100 were individuals with schizophrenia (n=100), 55 were patients with other psychoses (n=55), 315 were subjects with no psychotic disorders (n=315) and 10,464 were used as control subjects (n=10 464) (Riala et al. 2005). The study also examined associations between familial and environmental factors that could lead to smoking (Riala et al. 2005). The main result of the study was that the mean difference in time between the initiation of regular smoking and the onset of schizophrenia was 2.3 ± 6.6 which was significantly lower than the mean difference in time for subjects with other psychoses (8.6 ± 6.3) (Riala et al. 2005). As a result

of this short time period, Riala et al hypothesized that smoking maybe a sign of the prodromal phase of schizophrenia (Riala et al. 2005). This finding can be related to the self-medication model as it suggests that individuals with schizophrenia develop tobacco dependence as a result of the abnormal symptoms during the prodromal phase, which causes patients to use tobacco dependence as a form of relief from psychiatric symptoms.

The nascent calming effects of cigarette smoking in the schizophrenia population have been known to be one of the reasons why patients are motivated to smoke (Gurpegui et al. 2007). A study conducted by Gurpegui et al. compared the main reason for smoking among controls (n=100) and individuals with schizophrenia (n=173). The participants were interviewed using a questionnaire that examined the main reason for smoking by asking the subjects to answer the question "Why do you smoke" Gurpegui et al. 2007). The options included pleasure, calmness (anxiety-reducing), need, addiction, habit, entertainment and don't know Gurpegui et al. 2007) The Fagerstrom Test for Nicotine Dependence (FTND) was then used to classify smokers into mild dependence, high dependence and very high dependence groups Gurpegui et al. 2007). Patients with schizophrenia were also assessed on the Positive and Negative Syndrome Scale (PANSS) Gurpegui et al. 2007). The main reason for smoking was significantly different between the two groups ($\chi^2=92.09$, $df=6$, $P<.001$). The mean age of subjects with schizophrenia in the study was 35.5 ± 7.7 and the mean age of onset of daily smoking was 15.8 ± 4.2 Gurpegui et al. 2007). In subjects with schizophrenia, calmness as the main reason for smoking was more frequent than the comparison group Gurpegui et al. 2007). This study is also an example of self-medication. The transient calming effects of cigarette smoking may be perceived as especially attractive by patients since the symptoms of the illness not only cause immense anxiety and disturbance, but also cause a great deal of physiological stress.

Another reason why schizophrenia leads to smoking is because of the interaction of tobacco smoke with antipsychotic medication. Forchuk et al. conducted a study where it was hypothesized that individuals with schizophrenia are motivated to smoke not only because of the relief of psychiatric symptoms but also to gain relief from the side effects of antipsychotic medications (Forchuk et al. 2002). The research design included a descriptive, correlational design that assessed the relationships between medication

side effects; psychiatric symptoms and reasons for smoking and another component examined the content analysis of open-ended questions related to the subjective experience of smoking (Forchuk et al. 2002). The findings were consistent with the hypothesis because it was found that the strongest motivator to smoke was sedative effects ($M=2.32\pm.87$), control of negative symptoms ($M=2.10\pm1.05$), addiction ($M=2.09\pm1.00$) and control of side effects from antipsychotic medications ($M=1.85\pm.92$) respectively (Forchuk et al. 2002). These side effects in addition to the symptoms of schizophrenia can cause extreme difficulty in patients and since smoking has calming effects on the illness, it is also used to control the side effects of the medications. Although Forchuk et al shows that one of the reasons that schizophrenia patients smoke is to control side effects of antipsychotic medications, it must also be noted that the interaction of tobacco and antipsychotic medications alters antipsychotic blood levels (Ziedonis and George 1997), which then causes patients to require higher doses of the medication in order to gain effectiveness. Higher doses of antipsychotics can result to more side effects and as a result the patients will also have higher rates of tobacco dependence, which increases risks of other tobacco related illnesses.

In spite of the finding that smoking may be caused because of the symptoms of schizophrenia, many studies have reported that smoking can be one of the many environmental risk factors that cause schizophrenia. In a cohort study conducted by Weiser et al, a random sample of male adolescents ($n=14248$) was observed for the study (Weiser et al. 2004). Over a 4-16 year follow-up, it was found that adolescent smokers were at a greater risk for later schizophrenia and were significantly more likely to be later hospitalized for schizophrenia (Weiser et al. 2004). In addition, it was found that nicotine also activates mesolimbic dopamine neurotransmission that acts as reward (Weiser et al. 2004). This reward was important for adolescents who were beginning to show symptoms of a psychiatric illness.

In a study conducted by Spring et al, ($n=78$) the preferences for smoking cigarettes versus other social and pleasurable activities was assessed among patients with schizophrenia ($n=26$), patients with depression ($n=26$) and nonpsychiatric heavy smokers ($n=26$) (Spring et al. 2003). It was found that compared to smokers with no mental illness, smokers with schizophrenia and depression perceived cigarettes as more beneficial because of the great reward value than

alternative rewards for other activities (Spring et al. 2003). Although the reward value of smoking is of significance to schizophrenia patients, mesolimbic dopamine neurotransmission can increase the risk of psychosis in individuals who are already exposed to the other familial and environmental risks of schizophrenia (Weiser et al. 2004). Thus, it can be hypothesized that smoking in individuals with schizophrenia who are at a high risk for the illness due to other factors, can be a sign for the development of schizophrenia.

Although the factors associated with cigarette smoking can be analyzed at almost any point of the illness, adolescence is a critical time to evaluate cigarette smoking because the initiation of smoking occurs around age 15 (Rohde et al. 2003). In most cases, cigarette smoking also occurs before the onset of the illness (Rohde et al. 2003). Many studies have validated that the onset of schizophrenia occurs around age 18. The fact that the initiation of smoking occurs almost 3 years prior to the onset of the illness could possibly be explained by familial influence, substance abuse and also the nicotinic neurotransmission that is involved in the pathophysiology of schizophrenia (Weiser et al. 2004).

Rohde et al conducted a study where participants ($n=941$) were interviewed at three time points, beginning at high school and at age 24 [20]. Lifetime diagnoses for any psychiatric problems were obtained at each assessment and biological parents and siblings were interviewed to determine regular smoking and lifetime psychopathology (Rohde et al. 2003). The study concluded that adolescents of parents who smoked regularly or had any substance abuse were more likely to initiate smoking at an earlier age (Rohde et al. 2003). In addition, a stable home environment with two biological parents or foster families may protect adolescents from substance abuse (Laukannen et al. 2008). Although this study did not specifically target individuals with schizophrenia, the results can be applied to the adolescents who are likely to develop schizophrenia because environmental and genetic factors play a major role in the development of the illness.

The results of the male adolescent sample examined by Weiser et al, also suggested that the number of cigarettes smoked before the onset of the illness was significantly associated with the risk of developing schizophrenia (Weiser et al. 2004). Compared to non-smokers, adolescents who smoked 1-9 cigarettes a day were 1.38 times as likely to be later hospitalized for schizophrenia and those who 10 or more cigarettes a day were

2.28 times likely to be later hospitalized for schizophrenia (Weiser et al. 2004). The data on the abnormalities in nicotinic transmission and the high prevalence of smoking in potential schizophrenia patients indicates that the impaired nicotinic neurotransmission maybe involved in the risk-factor for developing schizophrenia. (Weiser et al. 2004).

Substance abuse also increases the risk of developing schizophrenia (Korhonen et al. 2008). In addition, early onset of smoking is also seen as an indicator of substance abuse. A study conducted by Weiser et al screened 270,000 adolescents of which 50,413 were suspected of having behavioral or personality disorders (Weiser et al. 2003). These adolescents were also questioned about drug abuse and were followed for later hospitalization for schizophrenia (Weiser et al. 2003). It was found that 12.4% of the adolescents who self-reported drug abuse, were later hospitalized for schizophrenia (Weiser et al. 2003). This finding may indicate that since substance abuse increases the risk of schizophrenia, adding tobacco dependence to the risk- factors may further increase the danger of developing schizophrenia.

Adolescents are not only at a greater risk for developing schizophrenia because all the other risk factors are present, but they are also known to have greater cognitive deficits than adult schizophrenia patients (White et al. 2006). A study by White et al compared adolescents with childhood- or adolescent-onset schizophrenia (n=49) to adults with adult-onset schizophrenia (n=139), healthy adolescent volunteers (n=32), and healthy adult volunteers (n=240) (White et al. 2006). Both groups were examined early in the course of their illness and the control groups were matched to the case groups based on age and parental education (White et al. 2006). It was found that adolescent patients performed significantly worse than the adult patients on tasks of motor functions, language and working memory (White et al. 2006). This is an important finding because it is already known that many individuals with schizophrenia smoke to calm their cognitive deficits and it is very likely that many of these adolescents have initiated cigarette smoking to calm their cognitive deficits. However, it is also known that smoking increases mesolimbic dopamine neurotransmission, which can increase the risk of psychosis in individuals who are already exposed to the other familial and environmental risks of schizophrenia (Weiser et al. 2004). Thus, tobacco dependence poses a great threat to adolescents with schizophrenia because it causes

disease-related illnesses over time and also increases mortality (Zeidonis et al. 2008).

Another reason why adolescents who smoke are at a greater risk for developing schizophrenia is because during the prodrome phase, adolescents experience social withdrawal, odd behavior and also have poor school performance (Hollis 2000). This is when the initiation of smoking also begins as a form of self-medication. Although cigarette smoking may provide calming effects to adolescents during a period of affective distress, previous studies have shown that cigarette smoking can also increase the chances of hospitalization for later schizophrenia (Weiser et al. 2004). Therefore, the fact those adolescents begin to smoke during this period, maybe a likely indicator of serious mental illness such as schizophrenia.

Implications of tobacco dependence on schizophrenia

Tobacco dependence in schizophrenia can have many unwanted implications on the illness as well. According to a National Institute of Mental Health report, individuals with schizophrenia have shorter life spans and increased mortality rates compared with the general population. This increased morbidity and mortality can be attributed to tobacco dependence and other modifiable risk factors such as poor nutrition, obesity, sedentary lifestyle and poor health care (Dixon, Postrado, Delahanty, Fischer, & Lehman, 1999; Goff et al., 2005; Sokal et al., 2004). Moreover, patients have double the risk for cardiovascular heart disease and triple the risk for respiratory diseases and lung cancer (Lichtermann, Ekelund, Pukkala, Tanskanen, & Lonnqvist, 2001). Heavy smoking in this population is also associated with higher risks for substance abuse (Ziedonis et al., 1994).

Cigarette smoking also affects the metabolism and blood levels of some psychiatric medications. The reduced blood levels are caused by the induction of the P450 1A2 isoenzyme, which is not caused by the nicotine in the tobacco, but is caused by the polycyclic aromatic hydrocarbons of tobacco smoke. This reduced blood level that is caused by increased tobacco dependence also explains why many patients experience reduced side effects of antipsychotic drugs. Common medications used by patients that are affected by the lowered blood levels are olanzapine, clozapine, haloperidol, and Fluphenazine. Thus it is important for mental health professionals to take tobacco dependence into account while monitoring the patients' drug

dosage and increase effectiveness of the antipsychotic (Desai, Seabolt, & Jann, 2001).

Patients with schizophrenia often have financial hardships and tobacco dependence only adds to the expense as most patients smoke an average of 25 cigarettes a day (one pack), if not more. This financial burden makes it difficult for many patients to afford cigarettes despite the fact that they are addicted to them. Consequently, many psychiatric institutions offer cigarettes as token economy to reinforce good behavior in patients (Gustafson, 1992). This is a problematic implication because patients with schizophrenia receive treatment in a variety of setting such as state hospitals, residential facilities, psychiatric hospitals and day treatment programs. Such settings should allow for intensive smoking cessation treatments but because perceived high reinforcement value of cigarettes, many institutions are reluctant to ban smoking.

Lastly, but most importantly, adolescents who are at risk for developing schizophrenia and who begin smoking at an early age are more likely to be daily smokers later on and are also likely to suffer from the above-mentioned unwanted implications of tobacco dependence sooner than those who do not smoke (de Leon, 1996).

Conclusion

The models reviewed support the hypothesis that early initiation of smoking maybe a great risk factor for the early onset of schizophrenia. When adolescents with genetic and environmental risk factors for schizophrenia initiate smoking, they are becoming more susceptible to the disease as nicotinic neurotransmission increases tobacco dependence. Also, smoking can be a sign of the prodrome phase in adolescence because the initiation of smoking usually begins during that period. In addition, smoking can be seen as one of the major risk factors because the time difference between the age of initiation of smoking and the onset of the illness is shorter compared to non-smokers. Studies have shown that the onset of Schizophrenia is usually seen anywhere between early and late adolescence. Moreover, models also show that patients in the prodrome phase also begin smoking before the onset of the illness. Consequently, it is important to direct cessation programs for adolescents, who smoke, are in the prodrome phase and also have other risk factors for schizophrenia present. This may reduce the vulnerability to the illness and mortality rates that are later seen in this population because of tobacco dependence.

A review of the models associated with smoking and Schizophrenia repeatedly show that patients find cigarette smoking attractive because of its perceived cognitive calming effects, many studies also demonstrate that during early abstinence or cessation, patients suffer no worsening of their psychotic symptoms (George, Vessicchio, Termine, Bregartner, Feingold, Rounsaville, Kosten, 2002). Currently, treatment options for smokers with Schizophrenia include pharmacotherapy and counseling interventions. Although pharmacotherapy works even in the absence of counseling treatments, outcomes are enhanced when both are combined. Unfortunately, only about 5% of smokers who make an attempt to quit receive counseling (Williams et al. 2007). Additional treatment options include drugs approved by the Food and Drug Administration such as nicotine patch, nicotine gum, and nicotine nasal spray and nicotine lozenges. Past studies have proved that such treatment options may have particularly greater advantages for patients because it improves abnormal electrophysiological measures, saccadic eye movements and has an overall improvement in working memory as well (Adler, Hoffer, Wiser, Freedman, 1993). Moreover, nicotine treatments have a rapid onset of action, more immediate craving relief that closely resembles smoking (Williams et al 2007). These drugs are also easy to use which may be more attractive to this population as well.

This extensive review can be merited as one that combines the most recent findings in the field of tobacco dependence and schizophrenia. The studies that have been discussed are relatively recent and they provide some helpful theories about the relationship between schizophrenia and tobacco dependence. Another advantage about this review is that it takes into account almost every model proposed to explain tobacco dependence in patients with schizophrenia. Moreover, the review also touches upon possible treatment methods for this population. In spite of these merits, the review does hold considerable limitations as well. One of the major limitations of the study is that there is not enough research conducted in the field of adolescents with schizophrenia who are heavy smokers. This evidence would have been very constructive for this review as it would provide additional support for the hypothesis that adolescents with a risk for schizophrenia are a greater risk for heavy tobacco dependence. Another limitation of this review is that the review made a very small reference to the molecular and cellular neurobiology of nicotine. Much research is

needed in the molecular and cellular component of nicotine so better pharmacotherapy treatments can be discovered for this population.

The age of onset is a key prognostic factor in schizophrenia and identifying the modifiable predictors at the age at onset is crucial in this population (Compton, 2009). However, this may be a great challenge diagnostically because the prodrome phase does not have specific symptoms and it occurs two to three years before the psychotic symptoms begin to appear. This makes the early detection of Schizophrenia very difficult and smoking could be dismissed during this chaos. Studies in the past have also demonstrated that the vulnerability to schizophrenia may be associated with the vulnerability to start smoking. Consequently, more studies are required to be done on diagnostic features of the illness during the prodrome phase. Mental health professionals should heavily take into account the effects of cigarette smoking on the prodrome phase of the illness and prescribe treatments accordingly. Furthermore, research in this field can prevent lower life expectancy because of cancer, cardiovascular and respiratory diseases and the cognitive deficits of the illness.

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