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Nicotine Addiction in Schizophrenia, Availability of Better Treatment Options as are in General Population

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ABSTRACT: *This article reviews literature regarding smoking cessation in Schizophrenia population, its harmful effects on health, finances, role of mental health care providers and better available options for treatment as are in general population. This population not only smokes at higher rates, but also has higher nicotine dependence with lower cessation rates than general population, people of schizophrenia have truncated life span due to smoking related diseases and premature mortality compared with the general population. Contrary to traditional reasoning that this population is not motivated or able to tolerate smoking cessation, but there is extensive literature that negates such rationale, even provides better treatment options to address this huge public health burden. Our review will mainly focusing treatment options particularly drug Varenicline, that shows most effective and promising results in patients of schizophrenia for smoking cessation as in general population, moreover different combination therapies, few new interventions, as well as some clinical areas will be discussed those need to be studied further in future.*

Key words: *Schizophrenia, Varenicline, smoking, suicide, mental health*

INTRODUCTION

Smoking in Schizophrenia Population, it's Harmful Effects on Health, Finances, Influenced by Disease itself, Socio-Demography, and Mental Health Care System

The prevalence of smoking is exceptionally high (70% to 80%) within the schizophrenia population (Baker et al., 2006; Chapman et al., 2009; De Leon & Diaz, 2005; Dome et al., 2010; Leonard et al., 2001) compared to other psychiatric disorders (50%) and the general population (21%) (Fiore, 2008; "Quitting smoking among adults-United States, 2001-2010," 2011). The association of smoking with schizophrenia has been exhibited within the literature, including a meta-analysis by De Leon and Diaz 2005, which showed that individuals with schizophrenia are five times more likely to smoke than the general population and 1.9 times more likely than those suffering from other severe mental illnesses (De Leon & Diaz, 2005). Additionally, individuals with schizophrenia smoke heavily (Tidey, Rohsenow, Kaplan et al., 2005; Williams et al., 2010) extract higher nicotine than smokers in healthy individuals (C. Kelly & McCreadie, 1999; Olincy, Young, & Freedman, 1997; Williams et al., 2010) with high levels of nicotine dependence scores (De Leon & Diaz, 2005; D. Weinberger & Marenco, 2007).

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The schizophrenic population has a substantially increased risk for a higher mortality (Brown, BARRACLOUGH, & INSKIP, 2000; Goff et al., 2005; Hannerz, Borgå, & Borritz, 2001; Kelly et al., 2011a) The mortality risk is higher than that of the general population (Saha, Chant, & McGrath, 2007) resulting in about a 20-25% reduction in average life span in people with schizophrenia (Colton & Manderscheid, 2006; Hennekens, 2007; Newman & Bland, 1991). A meta-analysis shows a linear increase in mortality over a period of three decades with an increased mortality gap (median SMRs for the 1970s, 1980s and 1990s were 1.84, 2.98 and 3.2) (Saha et al., 2007). Furthermore, the rates of death due to cardiac and pulmonary disease among schizophrenics are significantly higher (Brown et al., 2000; Hannerz et al., 2001). Estimated figures express that cardiac-related deaths are 12 times higher in young smokers relative to non-smokers: hazard ratio (HR)=12.4, p=0.0005 (Brown et al., 2000; Kelly et al., 2011b).

Bushe et al. conducted a review of various studies on mortality and its causes in schizophrenia population, which found cardiac disease to be a major contributor, but surprisingly there were increasing figures of cancer in this population (Bushe, Taylor, & Haukka, 2010)**,** Aside from natural causes of death, suicide also plays an important role of higher mortality. A meta-analysis which estimated risk of suicide, which was almost 13-times higher in the patients of schizophrenia than the general population (Saha et al., 2007). Among schizophrenic patients, smoking has been linked as a trigger for earlier onset. For example, Kelly & McCreadie et al. found that the earlier the age that one starts smoking, the earlier the onset of psychotic illness

is in women (C. Kelly & McCreadie, 1999). Besides this link for earlier onset smoking and the early onset of an illness, smoking is associated with higher severity of the disease, expressed as a higher PANSS total score (Schwartz, 2007). Additionally, this is supported by a recent study by Rajeev et al., which found that smoking could pre-date the onset of illness. However, the relationship between nicotine dependence and duration of prodromal period is yet to be known (Krishnadas, Jauhar, Telfer et al., 2012).

Smoking among schizophrenics puts a significant financial burden not only on patients but also on society in terms of taxes and frequent hospitalization. A study estimated that this population consumes 27% of the monthly income of those residing in a high tobacco tax state (Steinberg, Williams, & Ziedonis, 2004), which is higher than those of the general population only with 10% (Gilpin et al., 2001). Such high rates of smoking in individuals with schizophrenia places them as vulnerable targets for the tobacco industry (Els, 2007; Prochaska, Hall, & Bero, 2008).

WHY DO THEY SMOKE?

Several hypotheses have been suggested to explain the high rate of smoking and low rate of smoking cessation among schizophrenics. For example, smoking may improve the sensory gating (Adler et al., 1998), which is abnormal in these patients. Thus, resulting in cognitive impairment (Kumari & Postma, 2005) and perhaps as an attempt to correct such cognitive impairments.

Schizophrenic patients smoke; a habit which is better explained by the popular historical postulation entitled, "self medication hypothesis." Here it states that smoking may help these patients to manage their positive and negative symptoms by compensating for the underlying neurobiological deficits associated with the disorder (Adler et al., 1998; Dome et al., 2010; Leonard et al., 2001; Matthews, Wilson, & Mitchell, 2011; Olivier, Lubman, & Fraser, 2007; Patkar et al., 2002). Contrary to the hypothesis is that smoking improves cognitive functioning, where few studies have suggested that there are actual changes in some cognition-related brain processes and thus, increases concentration, alertness, and speed of performance (AhnAllen et al., 2008; Depatie et al., 2002; Jubelt et al., 2008; Larrison-Faucher, Matorin, & Sereno, 2004; Myers et al., 2004; Smith et al., 2005).

Social factors like unemployment, low educational attainment, peer influence and lack of smoking cessation treatment in mental health systems may also contribute to the increased risk of smoking in this population (Ziedonis et al., 2008). Similarly, it has been observed that smoking within this population helps these individuals cope with stress and boredom (Mann-Wrobel, Bennett, Weiner et al., 2011). In addition, it has been posited that nicotine may be used in this population to overcome side effects of variable anti-psychotic medications (Kelly & McCreadie, 2000; Levin et al., 1996; McEvoy et al. , 1995).

Another hypothesis of "shared vulnerability" of nicotine and schizophrenia suggested that first-degree relatives of patients with schizophrenia are more likely to smoke (Esterberg, Jones, Compton et al., 2007) or an association between daily smoking and schizophrenia reflected a shared genetic vulnerability, in comparison to other addictions (De Leon & Diaz, 2012).

ROLE OF CAREGIVERS AND MENTAL HEALTH SYSTEM TO ADDRESS CIGARETTE ADDICTION

Several studies support the relatively less aggressive treatment of cigarette addiction in severely mentally ill patients. In a study to assess the rate of nicotine problems diagnosed by psychiatrists in routine clinical practice, it was found that only 9.1% of patients received treatment for nicotine dependence (Montoya, Herbeck, Svikis et al. , 2005). In spite of the well-known fact of high prevalence of smoking in patients of mental illness, psychiatric patients are often excluded from studies examining various strategies for smoking cessation (Gonzales et al., 2006).

In a study of community mental health centers, it was revealed that while the majority of psychiatrists ask the patients about their smoking habit, only 24% of them consider such information to be of major clinical value (Price, Ambrosetti, Sidani et al., 2007). Researchers and clinicians have come to expect lower rates of long-term cigarette abstinence subsequent to tobacco-dependence treatment, which is usually 25% or less at year 1, even with combination therapy (Fiore, 2008).

Moreover, many clinicians assume that their patients cannot tolerate cessation attempts due to the stress of withdrawal, which often leads to symptom exacerbation. However, various studies have provided enough evidence that patients can generally tolerate smoking cessation in the short-term without symptoms exacerbation (Dalack et al., 1999; Evins et al., 2001; George et al., 2002).

Kelly et al. suggested that patients with schizophrenia smoke heavily to overcome dopamine blockage produced by antipsychotics, an effect which could produce reward effects (Kelly & McCreadie, 2000). Schizophrenic patients smoke heavily once they begin treatment with typical antipsychotics (McEvoy et al., 1995). Others found typical antipsychotic medications can influence nicotine addiction and make smoking cessation difficult (McNeill & Owen, 2005). A single dose of Haloperidol in normal subjects could lead to significant increases in smoking with higher levels of nicotine in the following hour (Dawe, Gray, Russell et al., 1995). In accordance with these theories, chronic patients were advised by clinicians to smoke as a means of treating their illness and the side effects of antipsychotics (Kumari & Postma, 2005; Leonard et al., 2001; Sacco et al., 2004). Since it is now known fact that smoking is highly modifiable risk factor (Bobes, Arango, Garcia-Garcia et al., 2010) but its treatment often goes unaddressed by clinicians customarily in population of mental illnesses (Prochaska, 2010).

ARE THEY WILLING TO QUIT SMOKING?

Research suggests that an important factor in smoking cessation is motivation to quit. Motivation to change has been identified as an important construct in the smoking cessation process (Font-Mayolas, Planes, Gras et al., 2007). Little is known about motivation and readiness to change in smokers with schizophrenia, Studies found when individuals with schizophrenia asked about their plans for quitting, reports show low motivation to quit smoking. Dissimilarly the high rate of smoking is attributable to an unwillingness to quit. Addington et al. observed that a substantial proportion of schizophrenic subjects were motivated to reduce or to quit smoking (Addington, el-Guebaly, Addington et al., 1997). In a study of 60 smokers who were questioned about their smoking, the subjects reported the same reasons for quitting as the general population and more than half of the sample wanted to stop smoking (Addington et al., 1997). In schizophrenic populations, the chief reasons for quitting smoking could be because of health concerns and social influences, which ultimately reinforce these individuals to quit (Addington, El-Guebaly, Campbell et al., 1998). Therefore, an important role of such social and behavioral factors are fairly reasonable to provide base for adding behavioral support to pharmacological interventions for addressing nicotine dependence in this population (George & Krystal, 2000; Ziedonis et al., 2005).

A study by Etter et al. assessed the stages of change in smokers with schizophrenia. From writing this review, this proves to be the only study that provides a direct comparison amongst the general populace. The level of motivation to quit was similar in patients with schizophrenia and in the general population, which is encouraging

given the high levels of smoking prevalence and tobacco dependence in these patients. Among those who had previously quit, the odds were 6 times higher in the general population than in the schizophrenia group, reflecting that people with schizophrenia have a harder time quitting than those in the general population (Etter, Mohr, Garin et al., 2004).

Evin et al. observed that persons with schizophrenia are often highly motivated and persistent in their attempts to quit smoking despite having long histories of smoking and high levels of nicotine dependence. A double-blind placebo controlled Bupropion SR 2-year follow-up study showed that 86% of the subjects reduced smoking significantly by the end of the trial, which was defined as ≥ 30% reduction in expired CO and ≥ 50% reduction in cigarette numbers per day. These subjects also maintained at least 50% reduction in smoking by the end of a 2-year follow-up (Evins et al., 2004).

Likewise, results from other studies demonstrate that up to two-thirds of people with schizophrenia would ideally like to quit smoking. Approximately one third of that number was ready to quit in the subsequent 6 months, one third was ready in the next three months and one third reported "some other time." These results suggest that motivating people with schizophrenia to further cessation attempts might be feasible with the proper educational resources and treatment plan (Moeller-Saxone, 2008).

Another study conducted by Kelly et al revealed that 88% of schizophrenic smokers and 83% of normal controls reported trying to quit smoking for at least 24 hours (P = 0.33). Additionally, the schizophrenic smokers rated themselves as more motivated by extrinsic factors as compared to the non-schizophrenic cohort, possibly due to a greater social pressure rewards than normal individuals (Kelly et al., 2010). Others have also reported that people with schizophrenia have a heightened reward value of smoking cigarettes compared with controls (Spring, Pingitore, & McChargue, 2003).

Mann-Wrobel, Bennett et al conducted a study demonstrating the relationships between smoking history, motivation to change, and smoking cessation outcomes in people with schizophrenia who smoke. This research was compiled from a database of a larger randomized trial involving the subjects with schizophrenia who smoke, taking a trial of Bupropion SR and a psycho-educational smoking cessation program. The subjects were followed for a 12-week period on medication and the placebo. Every subject attended 9 sessions of weekly smoking cessation group therapy. Over 75% of the subjects had made at least one 24-hour quitting attempt. On average, there were over 3 lifetime-quit attempts, although these were very short lived. Most participants reported wanting to quit smoking, but the sample generally reported low levels of confidence in their ability to quit (Mann-Wrobel et al., 2011).

In another study results were consistent with emerging evidence that percentages of smokers with schizophrenia and schizoaffective disorder who intend to quit smoking are quite similar to those of equally heavy smokers without psychiatric illness. The results of this study support the importance of focusing on the expected pros and cons of smoking in motivation, interviewing, and other cognitive behavioral interventions for tobacco dependence in people with schizophrenia (Tidey & Rohsenow, 2009).

VALIDITY AND RELIABILITY OF NICOTINE WITHDRAWAL AND WORSENING OF PSYCHIATRIC SYMPTOM

The high prevalence of smoking among those with schizophrenia, coupled with the clinical impression that smoking abstinence may to lead to an exacerbation of psychiatric symptoms, raises the need of measuring the validity and reliability of tests which could gauge the various effects of quitting smoking in schizophrenia while also helping to differentiate quitting effects from the emergence of psychiatric symptoms.

The scales and instruments commonly used to measure the quitting effects among schizophrenic patients are as follows:

1. Fagerstrom Test for Nicotine Dependence (FTND): six-item measure of nicotine dependence (range 0–10).

2. Minnesota Nicotine Withdrawal Scale (M-NWS): eight-item scale that assesses current symptoms of tobacco withdrawal including cravings and irritability (range 0–32).

3. Tiffany Questionnaire for Smoking Urges (TQSU): evaluates urges to smoke in response to positive (Factor 1) or negative (Factor 2) reinforcement (range 1–7).

Among these scales, the FTND has been shown to have high test-retest reliability in different studies (FTND test-retest reliability is high, r = 0.78 (Yang, McEvoy, Wilson et al., 2003), (M-NWS test-retest reliability, total score r = 0.71(Etter & Hughes, 2006). Measuring the internal consistency of these three widely used scales is important to use them as primary outcome measures.

There is a study by Weinberger et al. (Weinberger et al., 2007) which compared the smoking cessation outcome in smokers with schizophrenia and smokers without schizophrenia group of subjects using these three scales. The smokers with schizophrenia group of subjects (SS) was n=181 and the smokers without schizophrenia (CS) was n=151. The scales were performed at the baseline and follow-up. The results were as follows:

1. SS reported higher levels of nicotine dependence, greater symptoms of withdrawal, and higher endorsements of smoking related to negative reinforcement than CS.

2. The internal consistencies of the FTND, M-NWS, and TQSU Factor 2 were considerably high, yet did not differ significantly between the two groups. The internal consistencies of the TQSU Factor 1 were significantly lower for SS versus CS.

3. A high test-retest correlation was found for both CS and SS on average cigarettes per day (CPD measurement and CO ppm measurement). On the contrary, lower test–retest correlations were found for SS than CS on the FTND, TQSU Factor 1, and TQSU Factor 2. The test–retest of the M-NWS did not differ between the smoking groups.

For CS, the internal consistencies on all three smoking measures were high and comparable to previous research. Additionally, in the smokers with schizophrenia group, the internal consistency of these three measuring tests was not very high.

This study by Weinberger et al. has a sufficient number of subjects who were smokers with and without schizophrenia. Overall, the study suggests acceptable reliability of these standard smoking assessments for use in cigarette smokers with schizophrenia (Weinberger et al., 2007).

AVAILABLE TREATING OPTIONS FOR UNADDRESSED ISSUES IN SCHIZOPHRENIC POPULATION

As previously established, although the smoking rate is much higher in the schizophrenia population as compared to the general population, (Evins et al., 2004) clinicians do not often address smoking during patient interviews (Vokes, Bailey, & Rhodes,

2006). This issue pertains to many concerns, including the idea that treatment could worsen the patient's illness or that the patient is not willing to quit. However, both behavioral and pharmacologic cessation interventions are now available to these patients, which partially negate these hypotheses.

Stable patients with schizophrenia can tolerate cessation attempts without overall worsening of their illness and can have moderate short-term success in smoking cessation (Baker et al., 2006; Evins et al., 2000; Evins et al., 2005; Evins et al., 2007; Evins & Goff, 2008; Fatemi et al., 2005; George & Krystal, 2000; George et al., 2002; George et al., 2008; Weiner et al., 2001; Weiner et al., 2011).

Considering the willingness of these individuals, a breakthrough study done by Addington et al. after the smoking ban within hospitals showed that individuals with a long history of schizophrenia and heavy smoking expressed a strong desire to stop smoking, motivation to quit, and were able to tolerate smoking cessation attempts with convincing success. The study suggested an idea for future research, as smoking cessation is possible for the schizophrenia population, if the treatment is specifically designed for them (Addington et al., 1998).

A subsequent study by (Kelly & McCreadie, 1999) showed that one third of patients wanted to quit for health reasons, which is further supported by several other studies (Etter et al., 2004; Evins et al., 2004; Kelly et al., 2010; Mann-Wrobel et al., 2011; Moeller-Saxone, 2008).

NICOTINE REPLACEMENT THERAPY AND BUPROPION

Once individuals with schizophrenia are willing to quit their chronic nicotine addiction, different therapeutic options may prove to be beneficial. Their efficacy is yet to be examined within proper study settings. Considering safety and efficacy for different interventions, one early study (Ziedonis & George, 1997) done in 1997 by Ziedonis and George was done to assess the therapeutic effect of NRT in smoking cessation for individuals of schizophrenia. The study was not only limited to evaluate efficacy of NRT but also an assessment of a smoking cessation program, where 24 individuals with the diagnosis of schizophrenia participated in said study. 50% completed the 10 weeks program, 40% decreased use by 50%, and 13% remained abstinent for at least 6 months. The study included other interventions as well such as motivational enhancement therapy, and relapse prevention behavioral therapy as a part of the treatment. The author concluded and suggested there was a critical role of NRT and other adjunctive therapies for future research and for better outcomes of smoking cessation programs (Ziedonis & George, 1997). Following Ziedonis and colleagues a study done in 1998 by Addington where 50 outpatients with the diagnosis of schizophrenia were given nicotine patches and group therapy in a smoking cessation program. 42% subjects stopped smoking at the end of the group sessions, 16% remained abstinent at 3 months, and decreased 12% at 6 months (Addington et al., 1998). Results of the study were comparable and supporting to the results by Ziedonis' 1997 study. However, these results were not consistent with quitting rates within the general population, but still encouraging for future interventions and evidence to support combination therapy of NRT with group sessions. Considering Nicotine Replacement Therapy, various forms of NRT as well as with adjunctive therapies have exhibited promising results (Dalack et al., 1999; Williams & Ziedonis, 2004) for smoking cessation in patients of schizophrenia. Although, it is important to note that the most difficult part of treating this specific population is to maintain quitting for longer durations.

In other available options for treating nicotine dependence in schizophrenia populations, Bupropion emerged as a potent anti-addictive therapy for smoking cessation due to its antismoking effect (Slemmer, Martin, & Damaj, 2000; Warner & Shoaib, 2005). In 1997, bupropion was approved as the first non-nicotine medication for smoking cessation. In 2009, the FDA labeled a "black box" warning for Bupropion due to its possible adverse effects such as suicidal thoughts, hostility, depressed mood, agitation and suicide attempts (Food, 2010). Primarily, Bupropion posses an important and principal action upon the withdrawal symptoms following smoking cessation: it may attenuate multiple withdrawal symptoms, as well as prevent relapse after smoking cessation (Warner & Shoaib, 2005). Given the certain properties of Bupropion and its plan of action, it's being used and investigated for smoking cessation in general populations as well as in patients of various mental illnesses.

The "American Journal of Psychiatry Clinical Guidelines" and the updated treatment recommendations from 2009 from the "Schizophrenia Patient Outcomes Research Team" (PORT) both recommend that people with schizophrenia who want to quit smoking should be offered Bupropion SR with group support and education (Dixon et al., 2010; Kreyenbuhl et al., 2010). Several studies on combination therapy have been done on BUP SR, NRT and support group for smoking cessation or reduction in this population (Addington et al., 1998; Chou et al., 2004; Evins et al., 2001; Fatemi et al., 2005; George et al., 2002; Weiner et al., 2001). Yet aside from applying various interventions and different combinations, this population continues to smoke (Montoya & Vocci, 2007).

In 1999, Evins et al. reported the first case of Bupropion used in a study setting in patients with schizophrenia (Evins & Tisdale, 1999). In this case, a 41-year-old patient with schizophrenia was under treatment with the second-generation of the antipsychotic, clozapine. The subject was given Bupropion SR, and after a mere one week of treatment, the subject reported that he stopped smoking completely. He then continued the treatment with Bup SR for the next 7 months and remained abstinent for 11 months. It's important to mention that the patient remained stable during the study without any worsening of neuropsychiatric symptoms.

In 2001, Weiner et al. reported an open label pilot study that focused on sustained-released bupropion levels as well as group psychotherapy for smoking cessation in individuals with schizophrenia. The author examined efficacy, tolerability, and the safety of group psychotherapy with an adjunctive sustained-release bupropion for smoking cessation in patients of schizophrenia. Eight patients who received treatment for 14-weeks, had results that expressed a decrease in carbon monoxide levels without the worsening of neuropsychological symptoms. These results were very much encouraging for Bupropion use with group support in schizophrenic populations and warranted further studies on a larger scale. In the same year (2001) Evins et al. reported a first double-blind study of bupropion, where 19 stable outpatients participated in the study and were treated with sustained-release bupropion or a placebo, with cognitive behavioral therapy for 3 months and then a 3 month follow-up. Bupropion treatment showed greater reduction in smoking (66%) versus the placebo (11%) during active treatment of 3 months and the 3-month follow-up period. During the quit attempt, the Bupropion treatment compared to the placebo showed an improvement in negative symptoms and depressive symptoms. Following this study, the same author reported a larger double-blind placebo-controlled trial with 53 subjects with schizophrenia who were treated with bupropion or placebo for 12 weeks (Evins et al., 2005). The 7-day point prevalence abstinence quit rate was 36% in the bupropion group versus 7% in the placebo group. At the end of week 12, the quit rate of Bupropion group dropped to 16% versus 0% for the Placebo group. Another interesting finding was reported

that the Bupropion group had a higher 4-week continuous abstinence rate 16% versus 0% and maintained abstinence until the end of the intervention with longer duration of abstinence in Bupropion group versus placebo group.

After various studies on bupropion versus placebo, this drug was also studied with various combinations and showed more promising results than having it alone. In consideration of combination therapy, Evins et al. looked at the same components (Bupropion versus placebo), but it was reported on the basis of short-and long-term acting NRT (Evins et al., 2007). Subjects on the bupropion group showed a significantly higher smoking reduction rate versus the placebo group, but replenished rates were higher in both groups, and relapses were associated with tapering and discontinuation of treatment. This was due to a reduction in cigarette consumption under the combination therapy and higher relapses. The author suggested studying this population for long-term treatment with combination therapy.

A subsequent study (George et al., 2008) by George et al supported combination therapy with significant results in a double-blind study in which smokers assigned to the BUP+TNP group (n = 29) were more likely to achieve continuous smoking abstinence (8/29, 27.6%) than the PLO+TNP group (n = 29, 1/29, 3.4%) at 6-months post-TQD, 4/29 (13.8%) versus 0/29 (0.0%) achieved 7-day point prevalence smoking abstinence (p = .11). Neither Bupropion SR nor smoking abstinence significantly altered the positive or negative symptoms of schizophrenia. Combination therapy was well tolerated with modest side effects including poor concentration, lightheadedness, muscle stiffness and insomnia and, significantly, combination improved short-term smoking abstinence in smokers with schizophrenia (George et al., 2008).

Different Combination therapies like 'transdermal nicotine patch with sustained-release bupropion', or 'BUP with high dose NRT' showed more efficacy, were well tolerated, and superior to transdermal nicotine patch and placebo or NRT alone amongst schizophrenic populations (Evins et al., 2007; George et al., 2008).

In 2010 the Cochrane Collaboration determined that there was adequate evidence to support the role of bupropion SR for smoking cessation in people with schizophrenia (Tsoi, Porwal, & Webster, 2010). The study examined 21 randomized trials, and out of these seven trials compared bupropion with the placebo. A meta-analysis showed that smoking cessation rates *after* bupropion were significantly higher than the placebo at the end of the treatment (7 trials, N=340; risk ratio 2.84; 95% confidence interval 1.61 to 4.99; Dutra et al., 2011; Evins & Goff, 2008; Fatemi, 2008; Ismail et al., 2010; Weiner et al., 2011)and after six months (5 trials, N=214, RR 2.78; 95% CI 1.02 to 7.58). Expired carbon monoxide (CO) levels and the number of cigarettes smoked daily were significantly lower with bupropion at the end of the therapy, but not after six months. They concluded bupropion increases smoking abstinence rates in smokers with schizophrenia without worsening their symptoms, but their meta-analysis of trials comparing bupropion SR versus placebo did not reach significant results at the end of the treatment or even after the 6-month interval Intriguingly, another meta-analysis by Weiner et al in (Weiner et al., 2012) showed significant results for a 4-week abstinence. In this study, the pooled estimate of the odds ratio for the 4-week abstinence was 2.7, indicating that bupropion SR helps to improve the chance of successful quitting by almost 3-times that of the placebo. Importantly, there was no worsening of positive, negative, or depressive symptoms and there was no effect of abstinence on these symptom measures either (Weiner et al., 2012).

VARENICLINE AS AN EFFECTIVE, AFFORDABLE, SAFE AND A PROMISING AID

Varenicline is a partial α4β2 and full α7 nicotinic acetylcholine receptor agonist. In recent years Varenicline has been shown as an effective, safe and promising aid in treatment of smoking cessation within clinically stable patients of schizophrenia. Although Varenicline has been exclusively studied and used in healthy smokers, this drug has emerged as more effective than NRT and Bupropoin (Cahill et al., 2012; Jorenby et al., 2006; Mills et al., 2012) with higher quitting rates in comparison to both NRT and bupropion (Cahill et al., 2012; Eisenberg et al., 2008; Wu, Wilson, Dimoulas, & Mills, 2006) with limited role in relapse prevention (Cahill et al., 2012) yet to be studied in future on larger scale. Safety of varelcine has been questioned in recent years and a number of cases with neuropsychiatric adverse effects such as depression and suicidal thoughts were reported due to its use, after such reported cases, FDA labeled the drug with a black box warning in 2007 (Food, 2009). Contrary to such feared adverse effects about varenlcine, controlled trails published until the present date found this drug effective, affordable, safe and well tolerated in terms of neuropsychiatric adverse events, with a common possible side effect of mild to moderate nausea (Gonzales et al., 2006; Jorenby et al., 2006; Oncken et al., 2006; Stapleton et al., 2008; Tsai et al., 2007; Tsukahara et al., 2010; Wang et al., 2009).

In compare to healthy controls, Varenicline is not exclusively studied in patients of mental illness, particularly in high-smoking prevalent populations of schizophrenia. Safety and tolerability of Varenicline has been questioned in patients of mental illness, however there are many case reports (Anghelescu, 2009; Grosshans et al., 2009; Liu et al., 2009; Purvis et al., 2009) these reports provide fair evidence of varenciline tolerability without clinical worsening, in the same way a few small case series express similar outcomes (Evins & Goff, 2008; Smith et al., 2009; Weiner et al., 2011) which also reported good tolerance, and is further endorsed by larger clinical trails (Dutra et al., 2011; Hong et al., 2011; Liu et al., 2011; McClure et al., 2010; Pachas et al., 2012; Shim et al., 2011; Stapleton et al., 2008; Waldo et al., 2010; Williams, 2012).

Differing to safety and tolerability of Varenicline , there are certain case reports which show an increased risk of developing psychosis (Freedman, 2007), mania (Liu et al., 2009) paranoia (Ismail et al., 2010) and a depressed mood (Nino-Gomez et al., 2010).These adverse events with Varenicline use are not seen in many study settings and clinical trials for smoking cessation in schizophrenia populations (Hong et al., 2011; Smith et al., 2009; Tsoi et al., 2010).

One of early case series (Evins & Goff, 2008) in study settings by Evins & Goff examined 19 patients of schizophrenia treated on Varenicline . None of these patients dropped from the study had issues regarding the worsening of psychiatric symptoms; only 4 patients discontinued due to gastrointestinal symptoms, 13 out of 19 tolerated Varenicline and quit smoking between 10 to 21 days and continued to abstain smoking at 12 weeks. All 13 patients continued on Varenicline for the 24-week period to maintain abstinence and were closely observed. All patients remained clinically stable with no worsening of psychiatric symptoms (Evins & Goff, 2008).

Relatedly, there are few case reports, case series as well as larger prospective clinical trials conducted on patients of schizophrenia under treatment of Varenicline for smoking cessation. A double-blind randomized pilot study by Weiner et al (Weiner et al., 2011) examined 8 outpatients with schizophrenia or schizoaffective disease. 4 out of the 8 were treated with Varenicline and 4 were on placebo. 3 out of 4 were treated with Varenicline and 0 out 4 receiving the placebo sustained abstinence at week 12 without a significant worsening of psychiatric symptoms.

In addition to smoking cessation without worsening psychiatric illness, Varenicline has an aiding effect that produces improvement in ones mood and cognitive function (Patterson et al., 2009; Smith et al., 2009). Smith et al. did a small prospective study of 12 schizophrenic

smokers where Varenicline produced significant improvements in cognitive test scores. This was primarily associated with verbal learning and memory, but not in scores on visual-spatial learning or memory, nor on attention. Concurrently, it has a beneficial effect on smoking abstinence with no significant increases in psychopathology scores or clinical depression and suicidal ideation (Smith et al., 2009). Considering the effect of Varenicline on cognition, a double-blind study by Shim JC et al. (Shim et al., 2011) in which the author studied cognitive impairments amongst 120 stable patients with schizophrenia were treated with an adjunctive Varenicline . After the dropping of 3 patients, 117 were examined with the figure of 59 on Varenicline and 58 on placebo. Compared to the placebo, patients of Varenicline demonstrated significant improvements in the digit symbol substitution test (P=0.013) and Wisconsin card sorting test (non-preservative error, P=0.043). Similarly to Smith's 2009 study, none of the patients reported symptoms of depression or suicidal ideation. Though, both studies didn't identify significant improvement in overall cognition with the use of Varenicline. Thus, this important action of the drug has yet to be studied and sufficient data should be at place in order to understand its role in cognition.

Regarding efficacy and safety of Varenicline, a recent study (Williams, 2012) by Williams JM et al. had a 12-week, randomized, double-blind study, in which 84 participants received Varenicline and 43 received the placebo. They concluded that 19.0% met the criteria of smoking cessation for those on Varenicline versus 4.7% for placebo. William et al. found Varenicline was well tolerated without exacerbation of symptoms and had significantly higher smoking cessation rates versus the placebo. As for side-effects, few reported nausea, which was not that frequent due to the antiemetic property of antipsychotics, and irritability, anxiety and abnormal dreams which may be associated with the process of nicotine withdrawal (Williams, 2012).

Pachas et al. conducted a larger study (Pachas et al., 2012) with 112 stable individuals in an open labeled trial for outpatient smokers with schizophrenia and nicotine dependencies. These individuals participated for a 12 week smoking cessation trial of Varenicline and had weekly group cognitive behavioral therapy sessions. Participants showed increased abstinence rates and decreased symptoms of withdrawal as well as improvements in psychotic symptoms. At the end of the 12-week open label treatment, the 2-week and 4-week abstinence rates were 47% and 34% respectively. Those who were unable to quit sooner demonstrated a decrease in their smoking over time and the most common side effect observed during the study was nausea followed by anxiety, weight gain and paranoia. Regarding the use of Varenicline in general populations, there are common side effects which include nausea, insomnia, vomiting and abnormal dreams (Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2008; Tonstad, Davies et al., 2010) these adverse effects of Varenicline are nearly the same as observed in people of schizophrenia by its use (Evins & Goff, 2008; Pachas et al., 2012; Smith et al., 2009; Weiner et al., 2011).

The evidence of sharing common side effects and Varenicline tolerance in schizophrenic or general populations has an important implication: Varenicline could be highly capable in addressing this unfocused public health problem, while also potentially reducing higher rates of smoking in highly addicted, highly smoking prevalent schizophrenia populations. The most recent review paper (Cerimele & Durango, 2012) on the safety and tolerability of Varenicline by Cerimele JM et al. did a detailed analysis of 5 case reports, 1 case series, 1 retrospective study, 10 prospective studies and 1 meeting abstract, published reports to this present date express that Varenicline has been studied in patients of schizophrenia or schizoaffective disorder. Study determined out of 260 patients, only 13 patients (5% of the total) experienced the onset or worsening of any neuropsychiatric symptom, however 3 out 13 patients experienced a very brief negative effect after one dose, author concluded that no patients experienced suicidal ideation or suicidal behaviors (Cerimele & Durango, 2012). This analysis is further supportive and endorses that Varenicline is safe in most stable, closely monitored patients of schizophrenia without worsening of neuropsychiatric symptoms.

DISCUSSION

Currently, there are many interventions that have been tried to counter the major public health burdens of smoking either in general populations or in patients with mental illnesses, but this issue is not addressed more vigorously in patients with mental illness as in the general population. Despite having very high prevalence's of smoking in mental illness, particularly in the schizophrenic populations, this population often excluded from studies while applying and examining different strategies to counter this unmet health problem. Though we have observed successful regimens for smoking cessation in general populaces that have developed a significant decline in smoking prevalence.

For example, within general populations there is fair evidence that different combined therapies **(e.g. triple regimen therapy)** may also improve quitting rates and longer durations of treatments may also prove as successful outcomes (Steinberg & Greenhaus, 2009; Smith & McCarthy 2009, Piper ME, Smith SS 2009). Yet there is not any evidence-based data which could explain such examples of triple regimen therapy amongst patients of schizophrenia.

The efficacy, safety and tolerability of bupropion in schizophrenia populations could be more effective by adding other adjunctive therapies in that either group support, or NRT, there must be standardized assessment parameters to evaluate efficacy of various combinations that have been previously applied.

Relapse rates and maintaining abstinence for longer durations are difficult components of the smoking cessation treatment plans in this population. So, studies should be examined for longer durations and subjects should be treated for longer durations, which could improve overall outcomes by decreasing relapse rates, Though we have little evidence that Varenciline could be effective to prevent replase (Cahill et al., 2012), but future studies are needed to study varneicline particularly in this aspect.

Since Cognition dysfunction is one of major problem & has an important role in functional outcome of illness, couple of studies (Patterson et al., 2009; Smith et al., 2009) reviewed in this paper in those authors explained advantageous effect of Varenicline on cognition improvement, But there is need of further studies to evaluate any potential role of Varenicline on some or global improvement as well as cognitive measures are reflected in functional improvements in daily life.

Since Varenicline has black box warnings and there are certain case reports, which explain possible risks by its use, at the same time there are many evidence-based studies, which claim its efficacy and safe use. Thus, it is very critical to identify reliable predictors of good response or worsening of symptoms in order to minimize or maximize its efficacy and use, similarly these must be proper assessment (e.g. system, questionnaire, structured program) to assess suicidal ideations. These assessment types should also be considered for use in future studies similar to what William JM et al. did in a study (Williams, 2012).

Craving is an important factor in smoking, so newly emerging TMS treatment has shown good results for addressing this issue. There is a study (Wing, Bacher, Wu et al., 2012) by Wing et al.,

which has encouraging results and thus calls for further research to be done on larger scales .

Early deaths, short life span due to cardiovascular components or any other metabolic factor, should alert clinicians to increase the frequency of follow-up for these patients. Also, there should be a focus on preventing initial cardio-metabolic risks because subsequent reduction in this risk is more difficult to achieve, either through behavioral or pharmacologic interventions. Considering these facts and ignorance at the level of primary care health physicians, this issue should be addressed at the primary care level by regular assessments of the following factors: fasting glucose, body mass index, fasting triglycerides, fasting cholesterol, waist, high-density lipoprotein/low-density lipoprotein, blood pressure and symptoms of diabetes. In terms of interventions, most guidelines recommended advice on physical activity, diet, psycho-education of the patient, treatment of lipid abnormalities, treatment of diabetes, referral for advice and treatments, psycho-education of the family and smoking cessation advice.

Steinberg ML et al. did the first study, which examined the relationship between task persistence and smoking cessation outcome in smokers with schizophrenia. Task persistence may make important contributions to smoking cessation successful. This will be exhibited by indicating that the contribution of task persistence to smoking cessation is similar for smokers with schizophrenia and non-psychiatric smokers, which too, warrants more in-depth consideration on larger scales (Steinberg et al., 2012).

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