

# Approved and emerging smoking cessation treatments for people with schizophrenia spectrum disorders: A narrative review

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## Abstract

This review focuses on smoking cessation treatments for people with schizophrenia spectrum disorders. It concludes with comments on the significance of the research and why it constitutes an

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original contribution. We searched PubMed (National Library of Medicine), and PsycINFO (Ovid) (2006-2020) for studies on schizophrenic disorder (schizophrenia or psychotic or psychosis or severe mental illness) and smoking cessation treatment (smoking cessation treatment or varenicline or tobacco cessation or reduction or bupropion or NRT or behavioral treatment or e-cigarette). Studies found evidence suggesting that pharmacotherapy combined with behavioural therapy for smoking cessation is effective amongst smokers with schizophrenia spectrum disorders, although more long-term research is required. This review summarised and critically reviewed also studies on vaping as a smoking cessation strategy for smokers with schizophrenia spectrum disorders and evidence suggests that they may effective as smoking cessation tool and may be less harmful alternatives to combustible cigarette smoking. Consequently, e-cigarettes could be considered as an applicable instrument for Tobacco Harm Reduction (THR) and smoking cessation. Overall, there are very few studies of e-cigarettes for smoking cessation in patients with schizophrenia and these studies are very small. They have promising results, but more research is needed.

## Background

Tobacco smoking among people with mental illness is significantly higher than in the general population. Tobacco smoking has negative effects on physical, mental and financial well-being of people with mental illness (Molla *et al.*, 2017). In people with schizophrenia spectrum disorder, the risk of mortality is doubled (Bitter *et al.*, 2017). About 50% of deaths in patients with chronic mental illness are due to tobacco related cancers, respiratory diseases, and cardiovascular conditions (Callaghan *et al.*, 2014; Kelly *et al.*, 2011) and among smokers with schizophrenia spectrum, smoking is associated with depressive symptoms, increased hospitalizations, stress, poor treatment outcomes, low quality of life, and enhanced psychotic symptoms (Dixon *et al.*, 2007). Although smoking rates are declining in the general population in developed countries (Shafey *et al.*, 2010), patients with long-standing mental health disorders are almost twice as likely to smoke as people without such problems (Banham, 2010). Smoking prevalence rates among people with mental disorders are two to four times higher than in the general population (Tidey, 2005). Prevalence is greatest in patients with schizophrenia with rates around 64% followed by patients with bipolar disorder, with rates around 44% (Dickerson *et al.*, 2013). Smokers affected by schizophrenia spectrum disorders show an increase in rates of smoking and nicotine dependence relative to non-affected smokers. One possible reason for this phenomenon is that these patients smoke traditional cigarettes to stimulate their cognitive performance and several



studies have conducted to assess the impact of nicotine intake on cognitive function in people with schizophrenia spectrum disorder (D'Souza & Markou, 2012). However, the reasons for the high frequency of both high nicotine dependence and high smoking prevalence in patients with schizophrenia spectrum disorders are incompletely understood. Illness related factors, symptoms of illness factors, patient related factors and health service related barriers factors have been considered in an attempt to find a reason for the relationship between high smoking rates and schizophrenia but have failed to arrive at decisive conclusions. Environmental and genetic aspects play roles in the aetiology and progress of nicotine addiction and schizophrenia. Patient affected by schizophrenia have abnormal expression of certain genes which are common to nicotine addiction and schizophrenia disorder (Riley *et al.*, 2000; Mexal *et al.*, 2010; Purcell *et al.*, 2014; Owen Sawa & Mortensen, 2016). However, this does not completely explain the high smoking rates in smokers with schizophrenia spectrum disorders. Baker *et al.* (2007) reported that, compared to general population samples, persons affected by schizophrenia spectrum disorders were more likely to indicate that addiction, stimulation and stress management were reasons for smoking traditional cigarettes. McCloughen (2003) suggested that high smoking rates and high nicotine dependence in smokers with schizophrenia are explained by personal and social factors, many people with schizophrenia spectrum disorder are unemployed and inactive, and smoking was reported to relieve boredom and improve low self-esteem.

Kelly *et al.* (2012) examined the perceived consequences and benefits of cigarette smoking and motivation for quitting in 100 no treatment-seeking smokers who had schizophrenia or schizoaffective disorder and 100 people without a psychiatric disorder. People with schizophrenia reported that cigarette smoking made socialising easier compared with the control group. They also had a lower appreciation for health risks associated with cigarette smoking than controls. Potential health consequences were found to be a less compelling reason to quit smoking compared with the control group. Smoking cigarettes is frequently socially accepted among smokers with schizophrenia spectrum disorders (Trainor & Leavey, 2017; Twyman, Bonevski, Paul, & Bryant, 2014) and many smokers with schizophrenia spectrum are not given smoking cessation treatment from health professionals providers (Goldberg, 2010; Trainor & Leavey, 2017). Two researchers found that smokers with schizophrenia spectrum were less likely to be advised to quit compared with smokers without schizophrenia spectrum disorders (Briskman, Bar, Boaz, & Shargorodsky, 2012; Duffy *et al.* 2012). Brown *et al.* (Brown *et al.*, 2015) studied the perceptions of mental health professionals in providing the "5 A's" (ask, advise, assess, assist, arrange) of smoking cessation advice to smokers with schizophrenia. Clinicians rated their perceived lack of interest among patients to initiate a smoking cessation treatment related to too time demanding to carry out 5 A's, insufficient staff and staff scepticisms about the value of the 5 A's as a great barriers preventing application of the 5 A's. Health service and mental health professionals have an important role in encouraging quit attempts and can guide the application of smoking cessation treatment in clinical practice (Prochaska, 2011) but several mental health professionals believe stopping smoking traditional cigarettes may worsen their patients' condition, and some mental health professionals' feel that they are taking away one of their patients only pleasures/enjoyment in life (Ratschen, Britton, Doody, Leonardi-Bee, & McNeill, 2009; Johnson, Moffat, & Malchy, 2010) hence health service and health professionals related barriers factors are other possible reasons explaining high smoking rates in people affected by schizophrenia spectrum disorders.

## Materials and Methods

PubMed (National Library of Medicine), and PsycINFO (Ovid) were searched with the assistance of a trained librarian experienced in developing search strategies for reviews. Concepts that made up the search were: smoking cessation and schizophrenia. The search was not restricted by language or geographical region, and was carried out by combining an exhaustive list of terms denoting schizophrenic disorder (schizophrenia or psychotic or psychosis or severe mental illness) AND smoking cessation treatment (smoking cessation treatment or varenicline or tobacco cessation or reduction or bupropion or NRT or behavioural treatment or e-cigarette). Additionally, reference lists of all included papers were checked for any citations missed by electronic database searching. Cohort and case-control study designs were considered eligible for inclusion. Cross-sectional studies, case series and case reports were included. The publication dates were limited to January 2006 to February 2020. Relevant articles were also searched in Scopus (Elsevier) to determine if they were cited by studies that previous searches had not found. We identified 77 original studies from the electronic search of the databases (39 studies from PubMed and 38 from PsycINFO).

## Licensed aids to smoking cessation in smokers with schizophrenia spectrum

Actual licensed aids to smoking cessation in smokers with schizophrenia spectrum disorders still yield low long-term abstinence rates (Cather, Pachas, Cieslak, & Evins, 2017) and a meta-analytic study showed that for randomised controlled studies using bupropion or bupropion combined with NRT, the odds of smoking abstinence at six months were less than one in five participants (Tsoi, Porwal, & Webster, 2013).

## Nicotine replacement therapy

Seven studies evaluated NRT for smoking cessation in smokers with schizophrenia spectrum disorders.

Four observational studies of open label NRT plus psychosocial treatment with motivational interviewing and CBT components have been conducted in smokers with schizophrenia. Three studies in 24-65 outpatients found quit rates of 9-14% at six-month follow-up assessments (Ziedonis & George, 1997; Addington, el-Guebaly, Campbell, Hodgins, & Addington, 1998; George *et al.*, 2000) and one study in 68 outpatients found a 23% continuous abstinence rate at three-month follow-up (Chou, Chen, Lee, Ku, & Lu, 2004).

In the largest smoking study in this population, 298 outpatients with a psychotic disorder (57% with schizophrenia) were randomised to routine care or to 10 weeks of treatment with motivational interviewing and CBT plus NRT (Baker *et al.*, 2006). At the 12 month follow-up assessment, abstinence was not significantly higher in the treatment group (10.9%) compared with the control group (6.6%) (OR 1.72, 99% CI 0.58 to 5.09), but significantly more people in the treatment group had reduced the number of cigarettes they smoked each day by half (2.09, 99% CI 1.03 to 4.27). In addition, authors affirmed that the study groups showed significant improvement as a whole on several mental health questionnaires and absence of exacerbations of psychotic symptoms, but they used mental health questionnaires not specifically validated

for schizophrenia spectrum disorders.

One placebo-controlled study investigated the efficacy of NRT for the prevention of relapse in smokers with schizophrenia (Horst, Klein, Williams, & Werder, 2005). Fifty outpatients received nicotine patches that delivered 14-42 mg per day for 90 days along with weekly group motivational support. Those who quit (36%) were then randomised to continue receiving nicotine patches (same dose) or to receive placebo patches, along with biweekly group support, for another six months. At the end of this period, significantly more people receiving NRT remained abstinent compared with those receiving placebo (67% v 0%;  $P < 0.01$ ). However, the use of a high-level nicotine patch at 42 mg, although it can guarantee high levels of efficacy, makes the symptoms of nicotine overdose highly probable in cases where the subject continues to smoke.

In a Cochrane review that included 11 NRT studies, Tsoi *et al.* (2013) concluded that there is currently little evidence to support the effectiveness of NRT in people with schizophrenia despite the benefits in the general population.

## Bupropion

Eight studies evaluated bupropion for smoking cessation in smokers with schizophrenia spectrum disorders.

Two placebo-controlled trials in 32 and 57 smokers with schizophrenia found that bupropion significantly increased continuous abstinence during treatment ( $P < 0.05$ ), although these effects were not maintained at the three to six-month follow-ups (George *et al.*, 2002; Evins *et al.*, 2005). Two trials that compared bupropion plus NRT with placebo plus NRT in smokers with schizophrenia found that bupropion plus NRT significantly increased the odds of continuous abstinence during treatment but not at the three to 12 month follow-ups (D'Souza *et al.*, 2012; Esterlis *et al.*, 2013).

In an observational study that examined the efficacy of extended open label bupropion plus NRT, 41 smokers with schizophrenia received bupropion plus NRT (patch plus gum or lozenge) and CBT for three months. At the end of this period, those who were abstinent (42%) entered a 12 month relapse prevention phase with bupropion plus NRT and CBT (Cather *et al.*, 2013). At the 12 month assessment, 59% had achieved four weeks of continuous abstinence. However, the four previous trials and the observational study based their conclusions on studies that used small sample sizes. A Cochrane review by Tsoi *et al.* (2013) found that bupropion was associated with a three-fold increase in cessation in smokers with schizophrenia (risk ratio 3.03, 1.69 to 5.42 at end of treatment; 2.78, 1.02 to 7.58 at six months). In a recent systematic review and meta-analysis conducted by Peckham, Brabyn, Cook, Tew, and Gilbody, (2017), eight trials comparing bupropion with placebo were pooled showing that bupropion improved quit rates significantly in the medium and long term but not the short term (short term RR=6.42 95% CI 0.82–50.07; medium term RR=2.93 95% CI 1.61–5.34; long term RR=3.04 95% CI 1.10–8.42).

In the Evaluating Adverse Events in a Global Smoking Cessation (EAGLES) study (Anthenelli *et al.*, 2016), the largest comparative study of licensed smoking cessation aids, 8,144 smokers of traditional cigarettes with or without a diagnosis of psychiatric disorder used three months of treatment or placebo with a further three months follow-up of non-treatment, showing that bupropion has superior continuous abstinence rates vs. placebo at weeks 9-12 and 9-24 in both cohorts. 4,116 smokers were in the psychiatric cohort and 9.5% were affected by schizophrenia

spectrum disorders. However, the continuous success rates at week 12 and week 24 were larger for people without diagnosis of psychiatric disorders (week 12, 22.6%, week 24, 16.2%) compared with participants with psychiatric disorders (week 12, 26.1%, week 24, 18.8%) and success rates were not stratified according to the specific psychiatric diagnosis.

## Varenicline

Seven studies evaluated varenicline for smoking cessation in smokers with schizophrenia spectrum disorders.

A placebo-controlled trial ( $n=9$ ) found that three in four smokers with schizophrenia taking varenicline achieved continuous abstinence during the last four weeks of the treatment period compared with no patients taking placebo ( $P=0.14$ ) and no increases were seen in psychiatric symptoms or suicidal ideation (Weiner *et al.*, 2011). However, this research enrolled only nine participants, of which eight completed the study, and specific validated questionnaires for schizophrenia spectrum disorders, such as SAPS, SANS or PANSS, were not used to assess changes in schizophrenia symptoms. A multi-site placebo-controlled trial of varenicline with brief counseling in 128 smokers with schizophrenia found that varenicline significantly increased point prevalence abstinence at the end of treatment (19% v 4.7%;  $P < 0.05$ ) but not at the six month follow-up (Barr, Procyshyn, Hui, Johnson, & Honer, 2008). However, it is important to clarify that these patients undertook 12 weeks of treatment with varenicline and an extension of the use of varenicline up to 24 weeks would have probably reduced relapse rates at six month follow-up. In the study of Barr *et al.* (2008), rates of adverse events (AEs) were similar across conditions, and schizophrenia symptoms, assessed by SAPS and SANS scales, were stable or decreased in both groups.

Finally, a 10-site placebo-controlled trial investigated whether varenicline reduces smoking relapse (Evins *et al.*, 2014). In total, 247 patients with schizophrenia spectrum or bipolar disorder were enrolled and 203, of which 185 (91%) with schizophrenia spectrum disorders, entered the open label treatment phase. Of these, 87 (43%) attained two weeks of continuous abstinence and entered the relapse prevention phase, in which they were randomised to varenicline or placebo with CBT. At week 52, point prevalence abstinence rates were significantly higher in people taking varenicline (60% vs. 19%; OR 6.2, 95% CI 2.2 to 19.2), and rates of continuous abstinence from week 12 to 76 were also higher (30% vs. 11%; 3.4, 1.02 to 13.6). Varenicline had no effect on psychiatric symptoms. Two patients in each group reported suicidal ideation during the maintenance phase but there were no suicide attempts. Thus, amongst smokers with schizophrenia who attained abstinence, varenicline was well tolerated and increased prolonged abstinence for as long as 76 weeks (Evins *et al.*, 2014). However as declared by the authors, smokers were enrolled from community mental health centers so that the findings should be generalizable to the large majority of patients with schizophrenia spectrum or bipolar disorders who are cured in this kind of setting.

The EAGLES study showed that varenicline has superior continuous abstinence rates vs. bupropion, NRT patch and placebo at weeks 9-12 and 9-24 in smokers with and without a history of psychiatric disorders with no significantly increased neuropsychiatric safety risk vs. placebo (Anthenelli *et al.*, 2016). However, the continuous success rates at week 12 and week 24 were larger for people without diagnosis of psychiatric disorders (week 12, 33.5%; week 24, 21.8%) compared with participants with psychiatric dis-



orders (week 12, 38%; week 24, 25.5%) and success rates were not stratified according to the specific psychiatric diagnosis.

The Cochrane review by Tsoi *et al.* (2013), found that varenicline is associated with an almost five-fold increase in cessation (4.74, 1.34 to 16.71 at end of treatment). In the review and meta-analysis by Peckham, *et al.* (2017), five trials comparing varenicline with placebo showed that the addition of varenicline improved quit rates significantly in the medium term (RR=4.13, 95% CI 1.36–12.53). A network meta-analysis about the effectiveness and tolerability of adjunctive pharmacotherapy for smoking cessation in adults with serious mental illness (Roberts, Evins, McNeill, & Robson, 2016) suggests that varenicline and bupropion are effective and tolerable for smoking cessation in adults with serious mental illnesses. A review by Kishi and Iwata (2015) pooled five RCTs and found that varenicline performed no better than placebo in achieving smoking cessation (RR 0.79, 95% CI 0.58–1.08,  $n=332$ ); however, these authors combined findings of studies where participants were recruited into studies to test varenicline for health outcomes other than smoking cessation/reduction.

## Behavioural interventions

Bennett, Wilson, Genderson, and Saperstein (2013) identified 11 studies investigating behavioural therapies in people with schizophrenia and found that in the short term these had good post-treatment abstinence rates of up to 42%. In addition, Bennett *et al.* (2013) found that these interventions were well tolerated by people with schizophrenia and found no evidence of deleterious impact on psychiatric symptoms.

A study of 87 people compared higher versus lower intensity behavioural treatment delivered by trained mental health clinicians — Treatment of Addiction to Nicotine in Schizophrenia (TANS) or Medication Management (MM) — in smokers with schizophrenia who received NRT for 16 weeks and found no difference on abstinence (Williams *et al.*, 2010). TANS was a high intensity treatment of 24 sessions (45 minutes) delivered over 26 weeks and MM was a moderate intensity treatment of nine sessions (20 minutes) delivered over 26 weeks that combined with NRT treatment significantly reduced smoking consumption in smokers with schizophrenia spectrum disorders. This study showed that mental health professionals can be trained to help smokers with schizophrenia spectrum disorders to maintain traditional cigarette abstinence.

Considering all these aspects, it is important to also investigate harm reduction approaches for smokers with schizophrenia spectrum disorders.

## Experiences of smoking cessation

A study conducted by Tulloch and collaborators (2016) explored quitting experience and concerns of 732 smokers, 430 with psychiatric illness (18 with schizophrenia spectrum disorders), in comparison with 302 without psychiatric illness. Participants, enrolled between June 2010 and March 2013 to participate in the FLEX (Flexible and Extended Dosing of NRT and Varenicline in Comparison to Fixed-Dose NRT for Smoking Cessation) trial, completed questionnaires assessing previously used cessation aids and concerns about their upcoming quit attempt. Smokers with schizophrenia spectrum disorders experienced distress and negative affect as the most common predictors

of smoking relapse. The quit methods used by smokers with schizophrenia spectrum disorders were transdermal NRT (72.2%), followed by NRT gum (11.1%), NRT lozenge (11.1%), NRT inhaler (11.1%), varenicline (11.1%) and bupropion (11.1%) compared with the following quit methods used by smokers without psychiatric illness: transdermal NRT (69.9%), followed by bupropion (43.6%), NRT gum (32.9%), varenicline (19.3%), NRT inhaler (12.9%), and NRT lozenge (8.2%).

Rae, Pettey, Aubry, and Stol, (2015) interviewed 16 participants with serious mental illness (six with schizophrenia spectrum disorders) who had participated in a clinical trial comparing two smoking cessation interventions, the first using NRT alone and the second using NRT, motivational interviewing and a peer support group. Findings from semi-structured interviews suggest smoking cessation experiences were influenced by positive experiences of NRT, though access to e-cigarettes or medications available in pill form (e.g., varenicline and bupropion) were considered more effective and easier to use. The intervention itself (such as the presence of smoking cessation aids and group support), Individual factors, (such as mental health, physical health, and substance use), and social-environmental factors (such as difficult life events and social relationships) influenced whether someone quit or not. The authors acknowledged several limitations in their study such as the small sample size, all participants coming from the same smoking cessation intervention, the researcher not being blind to the smoking cessation status of participants during the data collection and analysis, the interpretative nature of the results and the fact that the data were self-reported by participants and consequently subject to the effects of recall and social desirability, and the use of the seven-day period of abstinence and not continuous smoking abstinence criterion to differentiate quitters from smokers. Also, the authors did not differentiate the findings on the basis of the distribution of the mental pathology enrolled in the study (schizophrenia/schizoaffective disorder ( $n=6$ , 38%), depression ( $n=5$ , 31%), bipolar disorder ( $n=4$ , 25%), and anxiety disorder ( $n=1$ , 6%) and the thematic analysis did not give clear percentages of responses but used vague terms such as “many” and “some”.

Knowles *et al.* (2016) qualitatively explored the experiences of a small sample of 13 participants with serious mental illnesses, of which eight had schizophrenia spectrum disorders, who used a ‘bespoke smoking cessation’ intervention, compared with their experience of standard smoking cessation services. The authors, without specifying if participants were in a stable or unstable phase of their illness and without differentiating the findings on the basis of diagnosis, enrolled five people with bipolar disorder and eight with schizophrenia spectrum disorders). They found that this intervention was perceived positively because the bespoke intervention was more flexible and tailored compared with the previous standard smoking cessation programme.

In addition to the medication used, tailoring the smoking cessation support to the individual needs of the smoker affected by schizophrenia spectrum disorders may result in better outcomes.

## E-cigarettes for smoking cessation in people with schizophrenia spectrum disorders

While the number of studies examining e-cigarettes for smoking cessation in the general population is now fairly substantial, despite mixed conclusions, there are far fewer studies relevant to this topic that have been conducted with priority groups for smoking cessation. This includes people with schizophrenia spectrum

disorders: the population that is the focus of this thesis. This section reviews the existing published literature on this topic, firstly outlining findings of studies that have examined e-cigarettes as an intervention for smoking cessation in this group, and secondly outlining the prevalence and attitudes of people with schizophrenia spectrum disorder regarding e-cigarettes.

## Interventional studies

A small uncontrolled study conducted at University of Catania was the first study in the world to investigate the efficacy of e-cigarettes for smoking cessation/reduction in people with schizophrenia. In this early study, 14 smokers with schizophrenia spectrum disorders not motivated to quit smoking were recruited. Fourteen smokers were provided with an electronic cigarette kit and enough cartridges to last up to 12 weeks. They were advised to use the product ad libitum throughout the day, not to exceed a four cartridge/day maximum as recommended by the manufacturer of the product, a first generation "Categoria" e-cigarette, (Arbi Group Srl, Milano, Italy) loaded with 7.4 mg nicotine cartridges called "Original" cartridges. Participants were followed-up for one year. At each visit, participant eCO levels were recorded, study diaries were given to study personnel and unused study products were turned in. Overall, this study found that at the 52-week visit, 50% of smokers with schizophrenia who were provided with e-cigarettes for 12 weeks had reduced their smoking by 50%, and a further 14% had quit smoking completely with no increases in psychiatric symptoms (Caponnetto, Auditore, Russo, Cappello, & Polosa, 2013). These preliminary findings are noteworthy because none of the participants initially sought treatment for smoking. However, the study had a significant number of limitations, including the absence of a control group and a very small sample size.

Subsequently, Pratt, Sargent, Daniels, Santos, and Brunette, (2016) enrolled 21 outpatients with serious mental illness (schizophrenia, schizoaffective disorder, or bipolar disorder) who smoked at least 10 CPD, had a history of failed treatment-facilitated quit attempts, and were not involved in smoking cessation treatment. Participants were given second generation e-cigarettes (N-Joy brand) based on each participant's level of use of traditional cigarettes and directions on how to use them, and were evaluated weekly for one month. Authors declared that each e-cigarette cartridge was approximately equivalent to two packs of traditional cigarettes but they didn't mention the nicotine strength of the cartridges used in the study. Nineteen participants completed the study visit (10 with schizophrenia spectrum disorders, nine with bipolar disorder). The study found a significant smoking reduction with a mean self-reported decline in use of traditional cigarette from 192 to 67 cigarettes/week confirmed by CO reduction from 27 ppm to 15 ppm. There were some AEs reported: 58% of participants experienced mild and transitory side effects, including cough, dry/sore throat, nausea and dizziness. The study also examined participant's perceptions. In answer to open-ended questions, these smokers perceived e-cigarettes as enjoyable and satisfying, and they were willing to buy e-cigarettes; they also perceived e-cigarettes as healthier, useful to help them feel more accepted by non-smokers, and useful to avoid the unpleasant odor of burned cigarettes. In their conclusions Pratt *et al.* (2016) suggested that people with serious mental illness may find e-cigarettes an appealing alternative to traditional cigarettes but recommended that further RCTs with longstanding mental health conditions were needed. In a more recent study, Hickling *et al.* (2018) conducted a 24-

week pilot study to investigate the efficacy of a six-week free first-generation e-cigarette treatment to reduce traditional cigarette consumption in 50 smokers with severe mental illness not motivated to quit, including 42 (84%) participants with schizophrenia spectrum disorders. These smokers were offered free NJOY disposable e-cigarettes with 4.5% nicotine and were encouraged to replace traditional cigarettes with e-cigarettes as much as possible. A final follow-up visit for assessment was scheduled at week 24. At the end of the six-week free e-cigarette phase, 37% of participants had reduced their tobacco consumption and 7% had stopped smoking. Four weeks post this phase 26% of participants had reduced their tobacco consumption and 5% had quit to smoke traditional cigarettes. At final follow up (24 weeks), 25% of participants had reduced their tobacco consumption and 2% had quit to smoke traditional cigarettes. This study found good product acceptability and no negative impact on participants' mental health or significant AEs. However, the study had limitations, including that 16% of participants with bipolar disorder had their psychopathological changes assessed by the PANSS scale, which is designed to assess schizophrenia spectrum disorder symptoms and not bipolar disorder symptoms. In addition, as the authors acknowledged, the study was also limited by the fact that it involved the use of a first-generation e-cigarette, considered less effective in terms of blood nicotine delivery, and the use of a self-report method for various measures.

## Prevalence and attitudes towards e-cigarettes in people with schizophrenia spectrum disorders

In addition to a small number of intervention studies, there are also some data available on the extent to which schizophrenic smokers use e-cigarettes and their attitudes towards these products. For example, Miller, Wang, Wong, Paletta, and Buckley (2017) investigated the prevalence and attitudes of e-cigarette use in the USA amongst 60 inpatients and outpatients with schizophrenia or schizoaffective disorder diagnosis. Participants completed an anonymous, 10-minute, pencil-and-paper survey to evaluate the prevalence of and attitudes toward e-cigarette use, and use of e-cigarettes to help or hinder their psychopathology. The majority (70%) of participants were current smokers, of whom 83% smoked a mean of 15 CPD; 90% percent of participants were aware of e-cigarettes, 37% had used them, 7% were current users and 24% of never-users were considering using e-cigarette in the future. Thirty four percent of surveyed smokers believed that the health effects of e-cigarettes were less harmful than traditional cigarettes. Cost was the most frequently mentioned potential disadvantage of e-cigarettes (33%) and health improvements (39%), smoking reduction (37%), and quitting (37%) were the most commonly mentioned potential benefits. Smokers who were ever-users stated that traditional cigarettes were significantly more useful in reducing paranoia, anxiety, depression, and reduced concentration, than e-cigarettes. The authors suggested that e-cigarettes have modest significance to smoking cessation in smokers with schizophrenia spectrum disorders and concluded that their preliminary findings should be investigated in larger samples.

Chen *et al.* (2016) conducted a survey of smoking cessation treatment with 231 smokers with serious mental illness (33% with schizophrenia/schizoaffective disorders, 63% with mood disorders, 11% with post-traumatic stress disorder and eight percent with borderline personality disorder), 45 psychiatrists and 97 case workers in four community mental health centers in the USA. Fifty



percent of smokers showed an interest in using e-cigarettes to quit smoking and 22% reported current e-cigarette use. There were differences between patient and provider perspectives: despite 82% of patients reporting wanting to quit or reduce traditional cigarette smoking, 91% of psychiatrists and 84% of case workers stated that their patients were not interested in quitting; hence, psychiatric treatment providers perceive their patients to have no motivation to quit smoking. In contrast, their patients reported motivation to use and active use of e-cigarettes to quit smoking.

Sharma, Wigginton, Meurk, Ford, and Gartner (2017) conducted a qualitative study to analyze Reddit online lay discussions and assess motivations and limitations associated with e-cigarette use amongst people with self-reported mental illness, including nine smokers with schizophrenia. Their thematic analysis included 3,263 comments from 133 discussion threads. Motivations to use e-cigarettes amongst people with mental illness included self-medication, quitting smoking, freedom and control, as a hobby, for social connectedness and in response to caregivers and online communities. Some limitations of e-cigarettes use included that they were perceived to be an unsatisfactory substitute for traditional cigarettes and psychiatric medicines, drug interactions, nicotine addiction, risks of e-liquid, practical difficulties and cost.

## Conclusions

Studies found evidence suggesting that pharmacotherapy combined with behavioural therapy for smoking cessation is effective amongst smokers with schizophrenia spectrum disorders, although more long-term research is required. This review summarised and critically reviewed also studies on vaping as a smoking cessation strategy for smokers with schizophrenia spectrum disorders. Although e-cigarettes have not been proven to be totally safe, evidence suggests that they may be less harmful alternatives to combustible cigarette smoking. Consequently, e-cigarettes could be considered as an applicable instrument for Tobacco Harm Reduction (THR). Overall, there are very few studies of e-cigarettes for smoking cessation in patients with schizophrenia and these studies are very small. They have promising results, but more research is needed. The findings from these studies, conducted with first generation and second-generation e-cigarettes, suggests that the provision of e-cigarettes can significantly reduce traditional cigarette consumption and CO (Carbon Monoxide) expired breath without significant variations of psychopathological signs and symptoms and without showing significant and serious Adverse Events (AEs).

## References

- Addington, J., el-Guebaly, N., Addington, D., & Hodgins, D. (1997). Readiness to stop smoking in schizophrenia. *The Canadian Journal of Psychiatry/La Revue canadienne de psychiatrie* 42(1), 49-52.
- Addington, J., el-Guebaly, N., Campbell, W., Hodgins, D. C., & Addington, D. (1998). Smoking cessation treatment for patients with schizophrenia. *The American Journal of Psychiatry*, 155(7), 974-976.
- Anthenelli, R. M., Benowitz, N. L., West, R., St Aubin, L., McRae, T., Lawrence, D., Asher, J., Russ, C., Krishen, A., & Evins, A. E. (2016). Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *The Lancet*, 387(10037), 2507-2520.
- Baker, A., Richmond, R., Haile, M., Lewin, T. J., Carr, V. J., Taylor, R. L., et al. (2006). A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. *The American Journal of Psychiatry*, 163 (11), 1934-42.
- Baker, A., Richmond, R., Haile, M., Lewin, T. J., Carr, V. J., Taylor, R. L., et al. (2007). Characteristics of smokers with a psychotic disorder and implications for smoking interventions. *Psychiatry Research*, 150(2), 141-152.
- Bar, A. M., Procyshyn, R. M., Hui, P., Johnson, J. L., & Honer, W. G. (2008). Self-reported motivation to smoke in schizophrenia is related to antipsychotic drug treatment. *Schizophrenia Research*, 100(1-3), 252-260.
- Bennett, M. E., Wilson, A. L., Genderson, M., & Saperstein, A. M. (2013). Smoking cessation in people with schizophrenia. *Current Drug Abuse Reviews*, 6(3), 180-90.
- Brown, C. H., Medoff, D., Dickerson, F. B., Fang, L. J., Lucksted, A., Goldberg, R. W., Dixon, L. B. (2015). Factors influencing implementation of smoking cessation treatment within community mental health centers. *Journal of dual diagnosis*, 11(2), 145-150.
- Briskman, I., Bar, G., Boaz, M., & Shargorodsky, M. (2012). Impact of Co-Morbid Mental Illness on the Diagnosis and Management of Patients Hospitalized for Medical Conditions in a General Hospital. *The International Journal of Psychiatry in Medicine*, 43(4), 339-348.
- Caponnetto, P., Auditore, R., Russo, C., Cappello G. C., & Polosa, R. (2013). Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *International Journal of Environmental Research and Public Health*, 10(2), 446-61.
- Caponnetto, P., Polosa, R., Auditore, R., Minutolo, G., Signorelli, M., Maglia, M., et al. (2014). Smoking Cessation and Reduction in Schizophrenia (SCARIS) with e-cigarette: study protocol for a randomized control trial. *Trials*, 15(1), 88.
- Cather, C., Dyer, M. A., Burrell, H. A., Hoepfner B., Goff, D. C., & Evins, A. E. (2013). An open trial of relapse prevention therapy for smokers with schizophrenia. *Journal of Dual Diagnosis*, 9(1), 87-93.
- Cather, C., Pachas, G.N., Cieslak, K.M., Evins, A.E. (2017). Achieving Smoking Cessation in Individuals with Schizophrenia: Special Considerations. *CNS Drugs*, 31, 471.
- Chen, L. S., Baker, T., Brownson, R. C., Carney, R. M., Jorenby, D., Hartz, S., et al. (2016). Smoking Cessation and Electronic Cigarettes in Community Mental Health Centers: Patient and Provider Perspectives. *Community Ment Health*, 53(6), 695-702.
- Chou, K. R., Chen, R., Lee, J. F., Ku, C. H., & Lu, R. B. (2004). The effectiveness of nicotine-patch therapy for smoking cessation in patients with schizophrenia. *International Journal of Nursing Studies*, 41(3), 321-30.
- Dickerson, F., Stallings, C., Origoni, A. E., Vaughan, C., Khushalani, S., Schroeder, J., Yolken, R. H. (2013). Cigarette smoking among persons with schizophrenia or bipolar disorder in routine clinical settings, 1999-2011. *Psychiatric services*, 64(1), 44-50.
- Dixon, L., Medoff, D. R., Wohlheiter, K., Goldberg, C., Kreyenbuhl, R., Adams, J., et al. (2007). Correlates of severity of smoking among persons with severe mental illness. *American Journal on Addiction*, 16(2), 101-110.

- D'Souza, M. S., & Markou, A. (2012). Schizophrenia and tobacco smoking comorbidity: nAChR agonists in the treatment of schizophrenia-associated cognitive deficits. *Neuropharmacology*, 62(3), 1564-1573.
- D'Souza, D. C., Esterlis, I., Carbuto, M., Krasenics, M., Seibyl, J., Bois, F., et al. (2012). Lower  $\beta 2^*$ -nicotinic acetylcholine receptor availability in smokers with schizophrenia. *The American Journal of Psychiatry*, 169(3), 326-34.
- Duffy, S. A., Kilbourne, A. M., Austin, K. L., Dalack, G. W., Woltmann, E. M., Waxmonsky, J., & Noonan, D. (2012). Risk of smoking and receipt of cessation services among veterans with mental disorders. *Psychiatric services (Washington, D.C.)*, 63(4), 325-332.
- Esterlis, I., Bois, F., Pittman, B., Picciotto, M. R., Shearer, L., Anticevic, A., et al. (2013). In vivo evidence for B2 nicotinic acetylcholine receptor subunit upregulation in smokers as compared with nonsmokers with schizophrenia. *Biological Psychiatry*, 76(6), 495-502.
- Evins, A. E., Cather, C., Deckersbach, T., Freudenreich, O., Culhane, M. A., Olm-Shipman, C. M., Henderson, D. C., Shoenfeld, D. A., Goff, D. C., Rigotti, N. A. (2005). A double-blind placebo controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *Journal of Clinical Psychopharmacology*, 25(3), 218-25.
- Evins, A. E., Cather, C., Pratt, S. A., Pachas, G. N., Hoepfner, S. S., Goff, D. C., Achtyens, E. D., Ayer, D., Shoenfeld, D. A. (2014). Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. *JAMA*, 311(2), 145-54.
- George, T.P., Ziedonis, D.M., Feingold, A., Pepper, W.T., Satterburg, C.A., Winkel, J., et al. (2000). Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry*, 157, 1835-1842.
- George, T.P., Vessicchio, J.C., Termine, A., Bregartner, T.A., Feingold, A., Rounsaville, B.J., et al. (2002). A placebo-controlled trial of bupropion for smoking cessation in schizophrenia. *Biological Psychiatry*, 52, 53-61.
- Goldberg, J. O. (2010). Successful Change in Tobacco Use in Schizophrenia. *Journal of the American Psychiatric Nurses Association*, 16(1), 30-35.
- Hickling L.M., Perez-Iglesias R., McNeill A., Dawkins L., Moxham J., Ruffell T., et al. (2018). A pre-post pilot study of electronic cigarettes to reduce smoking in people with severe mental illness. *Psychological Medicine*, 1-8
- Horst, W. D., Klein, M. W., Williams, D., & Werder, S. F. (2005). Extended use of nicotine replacement therapy to maintain smoking cessation in persons with schizophrenia. *Neuropsychiatric disease and treatment*, 1(4), 349-355.
- Johnson, J. L., Moffat, B., & Malchy, L. (2010). In the shadow of a new smoke free policy: A discourse analysis of health care providers' engagement in tobacco control in community mental health. *International Journal of Mental Health Systems*, 4(1), 23.
- Kelly, D. L., McMahon, R. P., Wehring, H. J., Liu, F., Mackowick, K. M., Boggs, D. L., et al. (2011). Cigarette smoking and mortality risk in people with schizophrenia. *Schizophrenia Bulletin*, 37(4), 832-838.
- Kelly, D. L., Raley, H. G., Lo, S., Wright, K., Liu, F., McMahon, R. P., Heishman, S. J. (2012). Perception of smoking risks and motivation to quit among nontreatment-seeking smokers with and without schizophrenia. *Schizophrenia bulletin*, 38(3), 543-551.
- Kishi, T., & Iwata, N. (2015). Varenicline for smoking cessation in people with schizophrenia: systematic review and meta-analysis. *European archives of psychiatry and clinical neuroscience*, 265(3), 259-268.
- Knowles, S., Planner, C., Bradshaw, T., Peckham, E., Man, M-S., & Gilbody, S. (2016). Making the journey with me: a qualitative study of experiences of a bespoke mental health smoking cessation intervention for service users with serious mental illness. *BMC Psychiatry*, 16:193.
- McCloughen, A. (2003). The association between schizophrenia and cigarette smoking: a review of the literature and implications for mental health nursing practice. *International journal of mental health nursing*, 12(2), 119-129.
- Mexal, S., Berger, R., Logel, J., Ross, R. G., Freedman, R., & Leonard, S. (2010). Differential regulation of  $\alpha 7$  nicotinic receptor gene (CHRNA7) expression in schizophrenic smokers. *Journal of molecular neuroscience*, 40(1-2), 185-195.
- Miller, B. J., Wang, A., Wong, J., Paletta, N., & Buckley, P. F. (2017). E-cigarette use in schizophrenia: prevalence and attitudes. *Annals of Clinical Psychiatry*, 29(1), 4-10.
- Owen, M. J., Sawa, A., & Mortensen, P.B. (2016). Schizophrenia. *Lancet*, 388, 86-97.
- Peckham, E., Brabyn, S., Cook, L., Tew, G., & Gilbody, S. (2017). Smoking cessation in severe mental illness: what works? an updated systematic review and meta-analysis. *BMC psychiatry*, 17(1), 252.
- Pratt, S. I., Sargent, J., Daniels, L., Santos, M. M., & Brunette, M. (2016). Appeal of electronic cigarettes in smokers with serious mental illness. *Addictive behaviors*, 59, 30-34.
- Prochaska, J. J. (2011). Smoking and mental illness-breaking the link. *New England Journal of Medicine*, 365 (3), 196-198.
- Purcell, S. M., Moran, J. L., Fromer, M., Ruderfer, D., Solovieff, N., & Roussos, P., O'Dushlaine, C., Chambert, K., Bergen, S. E., Kähler, A., Duncan, L., Stahl, E., Genovese, G., Fernández, E., O Collins, M., Komiyama, N. H., Choudhary, J. S., Magnusson, P. K. E., Banks, E., Shakir, K., garimella, K., Fennel, T., DePristo, M., Grant, S. G. M., Haggarty, S. J., Gabriel, S., Scolnick, E. M., Lander, E. S., Hultman, C. M., Sullivan, P. F., McCarroll, S. A., Sklar P. (2014). A polygenic burden of rare disruptive mutations in schizophrenia. *Nature*, 506 (7487), 185-90.
- Rae, J., Pettey D., Aubry, T., Stol, J. (2015) Factors Affecting Smoking Cessation Efforts of People with Severe Mental Illness: A Qualitative Study. *Journal of Dual Diagnosis*, 11(1), 42-49.
- Ratschen, E., Britton, J., Doody, G. A., Leonardi-Bee, J., & McNeill, A. (2009). Tobacco dependence, treatment and smoke-free policies: a survey of mental health professionals' knowledge and attitudes. *General hospital psychiatry*, 31(6), 576-582.
- Riley, B. P., Makoff, A., Mogudi-Carter, M., Jenkins, T., Williamson, R., Collier, D., Murray, R. (2000). Haplotype transmission disequilibrium and evidence for linkage of the CHRNA7 gene region to schizophrenia in Southern African Bantu families. *American journal of medical genetics*, 96 (2), 196-201.
- Roberts, E., Evins, A. E., McNeill, A., & Robson, D. (2016). Efficacy and tolerability of pharmacotherapy for smoking cessation in adults with serious mental illness: a systematic review and network meta-analysis. *Addiction*, 111(4), 599-612.
- Sharma, R., Wigginton, B., Meurk, C., Ford, P., & Gartner, C. E. (2017). Motivations and limitations associated with lapin among people with mental illness: A qualitative analysis of Reddit discussions. *International journal of environmental*



- research and public health, 14 (1), 7.
- Tidey, J. W., Rohsenow, D. J., Kaplan, G. B., & Swift, R. M. (2005). Cigarette smoking to pography in smokers with schizophrenia and matched non-psychiatric controls. *Drug and Alcohol Dependence*, 80 (2), 259-265.
- Trainor, K., & Leavey, G. (2017). Barriers and facilitators to smoking cessation among people with severe mental illness: a critical appraisal of qualitative studies. *Nicotine Tob Res*, 19(1), 14–23.
- Tsoi, D. T., Porwal, M., & Webster, A. C. (2013). Interventions for smoking cessation and reduction in individuals with schizophrenia. *The Cochrane Database of Systematic Reviews*, 2.
- Weiner, E., Buchholtz, A., Coffay, A., Liu, F., McMahon, R. P., Buchanan, R. W., Kelly, D. L. (2011). Varenicline for smoking cessation in people with schizophrenia: a double-blind randomized pilot study. *Schizophrenia research*, 129(1), 94-95.
- Williams, J. M., Steinberg, M. L., Zimmermann, M. H., Gandhi, K. K., Stipelman, B., Budsock, P. D., et al. (2010). Comparison of two intensities of tobacco dependence counseling in schizophrenia and schizoaffective disorder. *Journal of substance abuse treatment*, 38(4), 384-393.
- Yann, S. & Marina, R. (2008). Genetics of nicotinic acetylcholine receptors: Relevance to nicotine addiction. *Biochemical Pharmacology*, 75, 323–333.

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