Clinical overview

How can we promote smoking cessation in people with schizophrenia in practice? A clinical overview

Stubbs B, Vancampfort D, Bobes J, De Hert M, Mitchell AJ. How can we promote smoking cessation in people with schizophrenia in practice? A clinical overview.

Objective: High rates of smoking and nicotine dependence are associated with increased physical comorbidity and premature death in people with schizophrenia. We conducted a clinical overview to establish how smoking cessation should be promoted in practice.


Results: A growing body of evidence supports pharmacological interventions to assist smoking cessation. The most promising evidence is for bupropion with several meta-analyses demonstrating its effectiveness. Currently, there is limited evidence demonstrating the effectiveness of nicotine replacement therapy (NRT) and varenicline, although this is likely to be due to the paucity of research. There are no consistent data to suggest that pharmacological interventions increase adverse events. Behavioural and psychosocial interventions also demonstrate promise, particularly when combined with pharmacotherapy. Careful monitoring of antipsychotic levels (in particular clozapine) is essential, and the promotion of physical activity may be useful to negate potential weight gain and diabetes risk following smoking cessation.

Conclusion: Evidence from systematic reviews and meta-analyses suggests that smoking cessation interventions are effective in people with schizophrenia, although more long-term research is required. Promoting smoking cessation should be given utmost priority in clinical practice, and we offer practical strategies to facilitate this.

Clinical recommendations

- From the frontline pharmacological interventions, bupropion demonstrates particular promise with several reviews and meta-analyses demonstrating its effectiveness without any consistent reports of serious adverse events.
- Patients should also be offered behavioural and psychosocial support to help stop smoking, and physical activity may also have a beneficial impact.
- In practice, we recommend that clinicians (i) assess the nicotine dependency, (ii) agree on the quit smoking momentum, (iii) provide smoking cessation counselling, (iv) offer pharmacological support (v) monitor medication, weight, metabolic markers and offer exercise.
Smoking cessation should be given utmost priority in clinical practice, and all members of the multi-disciplinary team should have a role in this. To be effective, it is important that clinical and in particular nursing staff are on board with smoking cessation interventions in clinical practice. More long-term research is required; this should consider the impact of stopping smoking on the patient’s weight and diabetes risk.

Introduction

There is now irrefutable evidence that people with serious mental illnesses (SMI) such as schizophrenia have a drastically reduced life expectancy compared with members of the general population (1, 2). Worrying, this gap appears to be widening (3, 4). Recent research has elucidated that physical comorbidities and in particular cardiovascular disease account for a significant proportion of this premature mortality (1, 2, 4). Although cardiovascular disease risk and premature mortality are multifactorial, antipsychotic medication (5), inequalities in healthcare provision (6) and modifiable lifestyle factors contribute. Smoking is one modifiable lifestyle factor that has been consistently implicated as an influential factor to this mortality gap (2, 7).

The harm associated with tobacco use

Smoking is the most common substance use disorder in people with mental illness, and prevalence rates are two to four times higher than members of the general population (8). People with SMI, including schizophrenia, engage in particularly high rates of smoking and are often heavy smokers (8–10). High rates of smoking are also seen in people experiencing their first episode psychosis (11) suggesting smoking begins early in schizophrenia most often when people have prodromal symptoms. Indeed, recent research suggests that prodromal symptoms may be linked as much with cigarette smoking as with cannabis (12). Research is required to develop interventions to prevent smoking in those at ultra-high risk of psychosis, those experience their first episode and people with established psychosis.

The deleterious effects of smoking seem particularly pronounced and burdensome among people with schizophrenia (7, 13). For example, Callaghan et al. (9) found in a large scale follow-up study covering approximately 1.7 million years that tobacco-related conditions accounted for roughly 53% of total deaths in schizophrenia. This included an increased risk of tobacco-related deaths from cancer (standardized mortality ratio (SMR), 1.30, 95% CI 1.3–1.4), cardiovascular disease (SMR 2.46, 95% CI 2.41–2.50) and respiratory diseases (SMR 2.45, 95% CI 2.41–2.48) (9). Moreover, people with schizophrenia who smoke have reduced health compared to those people with schizophrenia who do not smoke (14). Recently, evidence has demonstrated that smoking may have a detrimental effect on the working memory (15) and hippocampal volume (16) of people with schizophrenia.

Challenges in promoting smoking cessation in people with schizophrenia

Whilst significant progress has been made in reducing smoking rates in the general population, less of an impact has been made on smoking rates among people with mental health diagnoses (17) and it is apparent that the difference in smoking prevalence is widening (14). Smoking is perhaps the most significant and challenging modifiable lifestyle factor among people with mental illness, and it requires urgent attention among people with schizophrenia. Clearly, there are pertinent barriers that need to be overcome in order to successfully implement smoking cessation in people with schizophrenia. For instance, people with schizophrenia are likely to experience more pronounced neurobiological, psychosocial and financial barriers to stopping smoking than the general population (14). In addition, people with schizophrenia have lower appreciation of the health risks from smoking and are less motivated to quit compared to people without schizophrenia (18). There have previously been concerns that the mental health of people with schizophrenia may deteriorate if they stop smoking, but these concerns appear unwarranted if the patient is psychiatrically stable (19, 20). Moreover, the public health strategies used to curb smoking in the general population such as media campaigns and tobacco price increases appear to not be as effective among people with mental illness (21). Given the high financial cost of smoking driven by rising taxes worsens the already pronounced socio-economic disadvantages people with schizophrenia typically face. Thus, it is an ethical imperative to
Promoting smoking cessation in schizophrenia

attempt to reduce smoking and fund effective methods for smoking cessation in this group.

Considering the aforementioned factors, there is an urgent need to consider the most viable and effective interventions to achieve smoking cessation in people with schizophrenia and how these can be incorporated into routine clinical practice. Therefore, we conducted a clinical overview to provide relevant evidence to guide smoking cessation among people with schizophrenia in clinical practice.

Aims of the study

The current clinical overview had two aims:

i) To consider which smoking cessation interventions are viable and work among people with schizophrenia and consider how these can be implemented in clinical practice.

ii) Establish if there are disparities in the delivery of smoking cessation interventions among people with schizophrenia and explore strategies to overcome these.

Material and methods

Search strategy

To address the clinical overview aims, a systematic selective literature review of the published literature was undertaken. The electronic databases Embase, PubMed and CINAHL were reviewed from inception until November 2014 using the words ‘smoking cessation’ or ‘smoking’ and ‘mental illness’, or ‘serious/severe mental illness’ or ‘schizophrenia’.

Eligibility criteria and study selection

We considered observational cohort and intervention studies in addition to systematic reviews (with or without meta-analyses) that met the following criteria: (i) included people with schizophrenia (according to ICD-10 or DSM criteria) (ii) reported a smoking cessation intervention (of any type) including those reporting disparities in receipt. Where possible, inferences were made from systematic reviews and meta-analyses because these are the top of the hierarchy of evidence and considered the ‘gold standard’ (22).

Results

Implementing smoking cessation programmes in practice

It is the ultimate aim that smoking cessation interventions should seek to achieve long-term smoking cessation. Both the American (23) and European psychiatric association (8) have suggested that people with mental illness, including schizophrenia, will need additional support over and above what the general population would expect or require. In addition, it is essential that the multidisciplinary team considers the individual patient’s own condition and develops tailored interventions to their specific needs (8, 14). A key strategy for the effectiveness of smoking cessation interventions is to help move the individual to a place of readiness to quit (24). To be a success, it is essential that the individual patient is psychiatrically stable (8, 19).

Smoke-free Wards and engaging staff in smoking cessation efforts

Smoke-free wards discourage smoking and hence are a form of smoke-free promotion. Since July 2008, mental health facilities in England have been required by law to be smoke-free indoors and other countries have adopted similar policies. It appears that at the time most staff disagreed with smoke-free legislation and mental health premises faced particular challenges in rolling out smoke-free zones (25). However, despite the challenges, the smoke-free policies have generally been successful. Clearly, clinicians have an important role in helping patients quit smoking. However staff often hold strong views regarding smoking. For instance, one study demonstrated that many staff (60%) believe that they should smoke with patients, 54% believed that smoking had a therapeutic role, and 93% believed that patients would deteriorate without access to cigarettes (26). Indeed, nursing staff who smoke are more likely to believe that patients should be allowed to smoke and that smoking has a positive therapeutic option for patients (27). Thus, this demonstrates the importance of educating and including clinical and nursing staff in smoking cessation efforts are vital in ensuring these are effective.

What smoking cessations interventions work?

Pharmacological interventions. Current frontline pharmacological interventions to assist smoking cessation include nicotine replacement therapy (NRT), bupropion and varenicline.

Nicotine replacement therapy. A recent Cochrane review Tsoi et al. (28) concluded that there is currently little evidence to support the effectiveness of NRT in people with schizophrenia despite the benefits in the general population. Nevertheless, the authors (28) attribute that this is almost certainly
due to a paucity of studies investigating NRT among people with schizophrenia. An earlier review (19) also failed to identify any randomised control trials (RCTs) specifically investigating NRT among people with schizophrenia. More recently, Bennett et al. (29) identified three studies investigating NRT and report that cessations rates achieved ranged between 23.1% and 66% immediately post-treatment. The recent EPA guidelines (8) were optimistic about the benefits of NRT to assist in smoking cessation and state that there is promising evidence for its use in schizophrenia. Overall, the evidence for NRT is limited, but this appears to not be a reflection on its lack of effectiveness but more due to the absence of high-quality studies with adequate follow-up periods.

**Bupropion.** Banham and Gilbody (19) pooled data from five studies and found that bupropion is more effective than the placebo in achieving smoking cessation in people with SMI (predominantly people with schizophrenia, RR 2.77, 95% CI 1.48–5.16). The authors (19) note that this is comparable to bupropion effect size in the general population. An updated Cochrane review (28) reported a similar effect size for bupropion in achieving smoking cessation in people with schizophrenia in the short term compared to the placebo (RR 3.03, 95% CI 1.69–5.42, N = 7, n = 340) and at 6 months (RR 2.78, 95% CI 1.02–7.58, N = 5). The authors found no evidence of any deleterious or serious adverse outcomes (including suicide, self-harm or any significant deterioration on mental health symptoms) although some minor adverse outcomes were reported including headaches and insomnia, although these could be attributable to nicotine withdrawal. Other reviews have also concluded that bupropion is safe and effective in smoking cessation without exacerbating an individual’s psychotic illness (29, 30).

Overall, the evidence suggests that bupropion is effective in achieving smoking cessation. Despite concerns about bupropion’s possible impact on suicide, there are currently no data supporting this, nor are there data demonstrating it is associated with a worsening in psychiatric symptoms.

**Varenicline.** Both the EPA guidelines (8) and numerous systematic reviews have (14, 29) have stated there is reason to be optimistic for the potential for varenicline to assist smoking cessation, but the evidence base is limited to a small number of RCTs and open label studies. Indeed, Tsoi et al. (28) pooled two studies and demonstrated varenicline is effective in achieving smoking cessation in the short term (RR 4.74, 95% CI 1.34–16.71, n = 137). Longer term data are limited, but no significant differences in psychiatric symptoms were noted although there were two reports of patients feeling suicidal and clearly the potential adverse effects on psychiatric symptoms cannot be ruled out (Tsoi et al. 28). Most recently, Kishi and Iwata (31) pooled five RCTs and found that varenicline performed no better than the placebo in achieving smoking cessation (RR 0.79, 95% CI 0.58–1.08, n = 332). The authors also report that despite questions regarding its efficacy, it appears to be safe and they detected no difference in suicidal ideation between varenicline and placebo. However, this null result was recently questioned (32) due to concerns that three RCTs should not have been included in the pooling.

Overall, it appears that varenicline has potential to help achieve smoking cessation in people with schizophrenia but longer term RCTs are required. These should also take into account carefully the patients psychiatric symptoms, and in particular, those at risk of self-harm and suicide should be carefully monitored.

**Non-pharmacological interventions.** **Electronic cigarettes.** In the general population, e-cigarettes have gained popularity and have been proposed as a lower risk alternative compared to the possible side-effects of pharmacological interventions. A recent Cochrane review found two RCTs comparing e-cigarettes with and without nicotine and demonstrated that e-cigarettes have the potential to reduce long-term smoking in the general population (33). The authors (33) also conclude that there appears to be no definitive evidence demonstrating clear health risks associated with e-cigarette use. However, these are not without controversy. For instance, Grana et al. (34) commented that in the general population, introducing e-cigarettes into smoke-free environments may result in population harm if use of the product reinforces the act of smoking as socially acceptable or if its use undermines the benefits of smoke-free policies. Little research has considered the impact of e-cigarettes in people with schizophrenia. One prospective pilot study by Caponnetto et al. (35) demonstrated that a 50% reduction in the number of cigarettes per day after 1 year in seven of 14 (50%) participants. However, the trial (35) also demonstrated that adverse events were relatively common including nausea (2/14 14.4%), throat irritation (2/14 14.4%), headaches (2/14, 14.4%) and dry coughs (4/14 28.6%) although no changes in psychiatric symptoms were noted. Most recently, Prochaska & Grana (36) reported that
among 956 (including 255 with psychosis), electronic cigarette use increased over time and was not associated with changes in smoking status or reductions in the number of cigarettes per day. With these early findings in mind, clearly there is currently insufficient evidence to make specific recommendations regarding the effectiveness of electronic cigarettes to assist smoking cessation. Clinicians can consider e-cigarettes as a potential option to assist patients stop smoking and should carefully monitor any side-effects that arise, but clearly more research is required to consider the safety and effectiveness of e-cigarettes in mental health settings.

Exercise. Exercise has been proposed as an aid for smoking cessation in the general population and it may assist by alleviating cravings and withdrawal symptoms (37). Little research has, however, investigated the effectiveness of exercise as a smoking cessation aid in people with schizophrenia. In the only pilot study to date (38), patients with schizophrenia following an 8-week counselling and exercise intervention reported significant reductions in tobacco consumption (−50%) and carbon monoxide level expired.

Behavioural and psychosocial therapies. Aubin et al. (14) suggest that behavioural smoking cessation approaches among people with psychiatric diagnoses should be flexible, and offer realistic steps such as increasing readiness to quit, motivation and if necessary a number of mini-quits before the goal of absolute abstinence (39). A range of behavioural interventions may be employed, but perhaps the most common and simple is to offer smoking cessation advice. A number of meta-analyses have demonstrated that simply offering smoking cessation advice may be effective in increasing attempts and achieve some success in smoking cessation in the general population (40, 41). Often behavioural and psychosocial interventions are used in conjunction with pharmacotherapy. Indeed, Bennett et al. (29) identified 11 studies investigating psychosocial 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. (29) found that psychosocial interventions were well tolerated by people with schizophrenia and found no evidence that these directly had any deleterious impact on psychiatric symptoms.

Potential future approaches that may help promote smoking cessation in people with schizophrenia. Various treatments for smoking cessation are under investigation and include testing new drugs (ClinicalTrials.gov Identifier: NCT02230384), transcranial direct current stimulation (NCT02128919), online electronic decision support (NCT01779440), multifaceted behavioural group treatment including pharmacological support (NCT00960375) and walking as a behavioural strategy (NCT01635075). New approaches to behavioural interventions could indeed help to yield better cessation rates, particularly when combined with pharmacotherapy. Indeed, a multi-component trial is currently underway (42) attempting to meet this call. In this study, participants with schizophrenia or bipolar disorder will receive (i) weekly individual motivational therapy for 4–12 weeks, and (ii) a 12-week active treatment phase in which patients receive a one- or 2-week supply of medication (transdermal nicotine patches, varenicline or bupropion) with instructions on how to take it, in addition to group psychotherapy for smoking cessation.

Disparities in smoking cessation interventions. A recent systematic review and meta-analysis (43) found that people with mental illness (RR 1.02, 95% CI 0.94–1.11, n = 721 658) and SMI (RR 1.09, 95% CI 0.98–1.230, n SMI = 6894, n control = 552 228) receive comparable rates of smoking cessation advice to people without mental illness. Mitchell et al. (43) also found that people with schizophrenia received comparable rates of smoking cessation advice (RR 1.09, 95% CI 0.68–1.70, n schizophrenia 2452 n controls = 536 129). The authors argue that for the aforementioned high prevalence rates and harms from smoking in this population, comparable rates are not satisfactory. In a large cross-sectional study, Szatkowski & McNeil (44) reviewed the primary care medical records contributed to The Health Improvement Network (THIN) from 495 general practices across the UK which included 387 246 smokers without a mental illness and 690 smokers with schizophrenia. The authors (44) established that people with schizophrenia were more likely to have been prescribed smoking cessation medications in the past year to help them stop smoking than the smokers without a mental illness (9.24% vs. 6.73%). However, the authors established this higher prevalence of smoking cessation medications was not apparent after they took into account the number of consultations in each group. The updated analysis demonstrated that general practitioners prescribed smoking cessation medication on 4.37% of their consultations for smokers without mental illness whilst this was 2.75% per consultation among smokers with schizophrenia. Thus, although evidence is
preliminary, it appears that people with schizophrenia do not receive adequate smoking cessation interventions from clinicians that are proportionate to their needs.

Providing additional support when quitting smoking

Withdrawal symptoms. Withdrawal symptoms from stopping smoking are common among the general population and may include physical symptoms (e.g., palpitations, low blood pressure) and psychological reactions such as difficulties with concentration and sleep (8). These symptoms typically peak 24–48 h after stopping smoking and disappear after 10 days. In general, people with SMI appear to show more severe withdrawal symptoms (8) and support should be given in practice for these.

Review medication. Smoking has a strong influence on the metabolism of several psychoactive drugs (8). Aubin et al. (14) recommend that once smoking abstinence is achieved among people with schizophrenia, the treating psychiatrists should review the choice and dose of antipsychotic medication due to the influence of nicotine on drug metabolism which may impact different antipsychotic medications (14). This is exemplified by Cormac et al. (45) who demonstrated that following a local smoking ban, 41.7% of patients had plasma clozapine levels over 1000 µg/l compared to 4.2% before the ban was implemented. The authors thus suggest careful monitoring of plasma clozapine levels for at least 6 months after cessation with necessary adjustments made in prescriptions. The EPA guidelines (8) also recommend that clozapine levels should be carefully monitored when an individual stops smoking.

Weight gain and diabetes risk from smoking cessation. A recent meta-analysis in the general population demonstrated that people typically gain 4.67 kg (95% CI 3.96–5.38) 12 months after quitting smoking (46). Moreover, another meta-analysis demonstrated that in the general population, stopping smoking is associated with an increased risk of diabetes (RR 1.44, 95% CI 1.31–1.58, (47)). Given that there are already great concerns about weight gain and type 2 diabetes among people with schizophrenia (5), support should be given to people with schizophrenia that intend to quit smoking to help combat this potential weight gain. Very few studies have considered the weight and metabolic impact from stopping smoking among people with schizophrenia and future research should consider this. One possible method that may help combat weight gain during attempts for smoking cessation is increasing physical activity and improving their diet. Indeed, in the general population, there is promising evidence that exercise may be an effective aid to smoking cessation (37). The multidisciplinary teams (MDT) should therefore encourage exercise, because this may help appease potential weight gain, possibly aid smoking cessation and reduce increasing metabolic risk.

Additional considerations for highly nicotine dependent people. Finally, although many patients with schizophrenia are heavy smokers, there is a subset of patients with schizophrenia who are highly dependent on nicotine, who may have been unsuccessful multiple times in stopping smoking and will need additional support. This group may benefit from higher doses of NRT, and in this population, e-cigarettes may be a much less harmful alternative than smoking itself. Whilst the effectiveness of these is not clarified in this population, clearly these options appear to be safer than continuing to smoke.

Discussion

Following on from this extensive clinical overview, we have developed clear practical steps for clinicians to promote smoking cessation in clinical practice.

Steps for implementing smoking cessation in practice

First and foremost, it is essential that MDT make smoking cessation a priority and all members of the MDT should provide a consistent message to patients encouraging and empowering them to quit. To achieve this, MDT could consider the following steps.

Assess the nicotine dependency. The patients smoking status should be evaluated and documented including the degree of nicotine dependence. The Fagerström Test for Nicotine Dependence (FTND) (48) is internationally the most accepted assessment tool and may prove useful because the FTND measures the dependence as a dimensional parameter and represents the severity of the dependence on a continuum. The FTND assesses the severity of a smoker’s physical dependence on the basis of six questions that are intended to record the construct nicotine dependence one dimensionally. The FTND is analysed using a sum score, which ranges from 0 to 10 points and corresponds to dependence severity, as follows: very low or no dependence (0–2 points); low dependence (3 or 4
points); medium dependence (5 points); and high dependence (≥6 points). If the clinical setting makes it not feasible to use this test, at least two of its items (namely the time when the first cigarette is smoked in the morning and the number of cigarettes smoked daily) should be recorded because these parameters are known to correlate most strongly with the degree of nicotine dependence (48). The patient should also be asked about previous cessation attempts and possible drug treatment attempts. Assessment of nicotine dependence will help predict whether the smoker is likely to experience nicotine withdrawal on stopping smoking. The use of breath carbon monoxide (CO) can also provide a measure of a person’s smoking status, and the FTND correlates with CO levels (8).

Agree on the quit smoking momentum. All smokers should be advised to quit in a way that is clear and unambiguous and supportive and non-confrontational. The best time for cessation would be when the patient is in a stable phase, with no recent or planned changes in psychotropic medication use (37). It is important that the consequences of tobacco dependence are clearly discussed and that the information on the quit smoking process is given in detail, allowing the patient to actively participate and take ownership.

Provide smoking cessation counselling. There is preliminary evidence (49) that following the 5 A’s framework may have long-term benefits on smoking-related outcomes. The 5A’s framework includes (i) asking (ask patient to describe their smoking status), (ii) advising (provide clear, strong advice to quit with personalized messages about the impact of smoking on health), (iii) assessing (assess the willingness to make a quit attempt), (iv) assisting (recommend the use of approved pharmacotherapy and refer to cessation services) and (v) arranging (follow-up by assessing the smoking status every visit, reinforce/encourage cessation) (34, 50). The EPA advises that it is particularly important to prepare patients for what can be expected in terms of withdrawal, which may in the short term include restlessness and anxiety (8) and exercise may help ameliorate these potential side-effects (37). Furthermore, discussing alternative ways to cope with stressful situations and anxious feelings that may arise could improve outcome in these patients. If patients are unwilling to quit, then in order to help increase their readiness to quit, the ‘5 R’s’ motivational intervention could be employed (50): (i) relevance (ask the patient to identify why quitting might be personally relevant), (ii) risks (ask the patient to identify negative consequences from smoking), (iii) rewards (ask the patient to identify potential benefits and rewards of smoking cessation), (iv) roadblocks (ask the patient to identify barriers to quitting smoking), and (v) repetition (repeat the above strategies every time an unmotivated patient has a visit).

Offer pharmacological support. Drug treatment with a first-line product (bupropion, NRT and varenicline) should be given for even a mild degree of tobacco dependence. In the section ‘pharmacological interventions’, we discuss in great detail the research in this area. Based on the available current available evidence, we recommend that the frontline pharmacological intervention should be bupropion.

Monitor medication, weight, metabolic markers and offer exercise. As stopping smoking can lead to potentially pronounced alterations in psychotropic medication levels, MDTs should monitor medication levels (in particular clozapine) for at least 6 months after stopping smoking. Although data among people with schizophrenia are sparse, data from the general population consistently demonstrate concerns about increased weight gain and diabetes risk. Clinicians should also monitor these in practice and routinely recommend exercise to possibly ameliorate these concerns and possibly reduce cravings.

In conclusion, the evidence base for pharmacological interventions is limited but growing and bupropion appears to be particularly promising. To date, there is little evidence to suggest that pharmacological interventions have serious adverse effects on people with schizophrenia. There is also promising research for the use of behaviour and psychosocial interventions to promote smoking cessation particular when used in conjunction with pharmacological interventions. Perhaps the most effective strategy to combine pharmacological and psychosocial (in particular motivational) interventions and encouraging physical activity may help ameliorate the anticipated weight gain associated with stopping smoking cessation. In practical terms, we recommend that clinicians seek to (i) assess the nicotine dependency, (ii) agree on the quit smoking momentum, (iii) provide smoking cessation counselling, (iv) offer pharmacological support (v) monitor medication, weight, metabolic markers and offer exercise to ameliorate these potential factors and help with cravings.
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