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Smoking Cessation Interventions for Patients with Severe Mental Illnesses: A Review of Clinical Effectiveness and Guidelines

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Context and Policy Issues

While society as a whole has seen a drastic decline in smoking over the past few decades, people with a mental disorder have not had the same gains. Smoking among people with posttraumatic stress disorder (PTSD), for example, has been estimated at around 45%, with greater nicotine dependence and heavier smoking than the general population.[1] Among people with schizophrenia, the likelihood of smoking is more than five times greater than that of the general population.[2] In addition to the higher smoking prevalence, people with severe mental illness have premature mortality compared to the general population, a gap primarily driven by cardiovascular and respiratory diseases. These driving diseases have prompted calls for treating associated lifestyle factors including high smoking rates.[3]

Pharmacological interventions are available to assist in smoking cessation by reducing nicotine withdrawal. The main medications found to be effective are nicotine replacement therapy (NRT), varenicline and bupropion.[4] The first comes in patch, lozenge, gum, nasal spray and oral inhaler form, and provides nicotine without tobacco while the user breaks smoking behavior. Varenicline by contrast is an orally ingested partial agonist that binds to the nicotinic receptor to reduce cravings. Finally, bupropion was an anti-depressant that was subsequently licensed for smoking cessation. It is believed to act by enhancing noradrenergic and dopaminergic release.[4]

While there is some evidence of predisposition and more severe nicotine dependence among those with schizophrenia,[5,6] the observed low cessation rates among those with mental illness[7] are thought to be partly due to lower availability and/or utilization of pharmacotherapy.[8,9] People with mental illness are often excluded from large clinical trials,[10] so effectiveness in this group is not evident, especially in the context of particularly high smoking rates, relapse rates and nicotine dependence.[10] In addition, there is concern among smokers and clinicians that the medications are unsafe due to the potential for severe psychiatric reactions.[11] For example, post-marketing reports have suggested varenicline and bupropion may increase the risk of suicidal thoughts.[4]

Treatment may be able to lessen the significant burden and associated risks of smoking among people with mental illness, but concerns about effectiveness and safety may limit its potential. To inform decisions about using pharmacotherapy among those with mental illness, specific evidence is thus required. As such, this rapid review summarizes the evidence on the effectiveness and evidence-based guidelines on smoking cessation intervention among those with severe mental illness.

Research Questions

1. What is the clinical evidence regarding the effectiveness of smoking cessation interventions for patients with severe mental illnesses?

2. What are the evidence-based guidelines regarding smoking cessation interventions for patients with severe mental illnesses?

Key Findings

Nicotine replacement therapy (NRT), varenicline and bupropion were all generally found to improve smoking cessation rates, most commonly measured as 7-day point prevalence abstinence against placebo, among people with severe mental illness. Varenicline and bupropion may be more effective than NRT. The longest follow up duration on treatment was six months, and sustained effects beyond this were unclear, except in one study that did not find an increase in suicide attempts/behaviours after one year.

There was no evidence that adverse events occurred more often than in those without mental illness, or that psychiatric symptoms worsened. Nausea and sleep disturbances were common with varenicline. All studies included some form of psychosocial support in addition to the pharmacological intervention, and only one study considered randomizing different dosages for NRT, and did not find a difference. In general, the quality of studies was low and sample sizes small.

One guideline was found, which did not favour any treatment, but suggested considering NRT, varenicline or bupropion for patients with severe mental illness, with safety caveats for the latter two that may require closer patient monitoring.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and July 21, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients who are smokers and who have mental illnesses including schizophrenia, schizoaffective disorder, psychosis, bipolar disorder, other psychotic disorders and post-traumatic stress disorder (PTSD).
Intervention	Nicotine Replacement Therapy (NRT) Varenicline Bupropion Combination therapies that include either NRT or an oral drug
Comparator	Q1: Any comparator; No active comparator; Comparisons between those with and without mental illnesses

	Q2: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., length of time for success, doses that are successful) and safety (patient harms and benefits) Q2: Guidelines
Study Designs	Q1: Health technology assessments, systematic review, randomized controlled trials, non-randomized studies Q2: Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were published prior to 2006 or already appeared in a systematic review identified through the search. Articles where the primary focus was on patients with mood disorders such as depression and anxiety were also excluded as this was not the target population of interest.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR checklist,[12] clinical studies were critically appraised using Downs and Black,[13] and guidelines were assessed with the AGREE II instrument.[14] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

This report made use of a previous Rapid Response Reference List[15] on the same subject to identify studies, which was supplemented by an updated search. The original search, which was completed in July 2016, identified 325 citations, of which 25 were ordered for full-text screening. A total of 86 additional citations were identified in the literature search update. Following screening of titles and abstracts of the 86 new citations, 65 citations were excluded and 21 potentially relevant reports from the electronic search were retrieved for full-text review. Forty-five potentially relevant publications were retrieved from the grey literature search and, in addition to the 25 from the previous reference list on the topic and the 21 added in the update, 91 full texts were reviewed. Of these potentially relevant articles, 68 publications were excluded for various reasons, while 23 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest that didn't meet the selection criteria are provided in Appendix 5.

Summary of Study Characteristics

Details of the characteristics of individual studies are provided in Appendix 2.

Study Design

Eight systematic reviews were found. Two reviews retrieved 22 and 13 studies respectively, including pharmacological interventions, though did not specify study types or specific interventions.[16,17] The others included 17 studies representing 14 randomized controlled trials (RCTs) identified until December 2014,[8] 21 studies of seven RCTs until March 2009,[6] eight RCT studies identified until September 2015,[18] seven double-blinded, placebo controlled trials from a search up to August 2014,[19] and 34 randomized trials with 10 focused on pharmacological interventions identified up to October 2012.[20] Finally the most recent review with a search up to September 2016 included 28 RCTs of which 16 focused on pharmacological interventions.[21]

In addition to the systematic reviews, four double-blinded RCTs were found.[10,22-24] One of these was a pooled analysis of two RCTs with an open-label cessation phase, followed by a randomized, blinded maintenance phase.[10] There was also one open label RCT[25] and one secondary analysis of a blinded RCT.[26]

The remaining eight studies were non-randomized. In two cohort studies,[27,28] patients self-selected into the treatment and comparator groups, and two retrospective cohort studies were based on chart reviews.[29,30] Four pre/post studies where outcomes were compared over time in the same subjects before and after treatment were also included.[31-34]

One guideline published by the National Institute for Health and Care Excellence (NICE)[35] was found.

Country of Origin

The systematic reviews did not have country restrictions, though three were restricted to English language studies only.[8,16,21] Of the randomized studies, one was situated in Australia,[22] one in Taiwan,[23] two in the U.S.,[24,25] one was in Korea[26] and one was a multi-national trial.[10]

Among the non-randomized studies, two were from Spain,[28,31] one took place in the UK,[27] three from the U.S.,[29,32,34] one from Brazil,[30] and the remaining one was situated in Australia.[33]

The guideline was published by the United Kingdom's NICE.[35]

Patient Population

Systematic reviews

Four of the systematic reviews specified a restriction to adults, usually defined as 18 or older,[8,18,20,21] though in practice the studies included in the other reviews were also limited to adults. Three included only schizophrenia or schizoaffective disorder[6,20] or schizophrenia spectrum disorders,[17] while the other studies additionally included other disorders. One included people with bipolar disorder, delusional disorder and depressive psychoses, but in practice all but 3 of 17 studies were among people with schizophrenia or schizoaffective disorder.[8] Another review also included schizophreniform disorder and delusional disorder, though similarly, 6 of 7 studies ended up being with schizophrenia patients, and one included both schizophrenia and bipolar disorder patients.[19] The remaining two systematic reviews were more broad, with one specifying any severe mental illness[18] and the other including schizophrenia or other psychotic disorders, bipolar disorder and depression with psychotic features.[21] This last study specifically excluded those with PTSD, personality,

anxiety disorders, major depression and autism. One study only required 50% or more of a study sample to have schizophrenia or schizoaffective disorder.[16] Four systematic reviews specified the participants had to be smokers[6,8,17,20] and one further specified the patients had to have motivation to quit or reduce smoking.[8] While the others did not explicitly specify participants had to be smokers, in practice they were.

Clinical Studies

Five studies included only people with a diagnosis of schizophrenia or schizoaffective disorder.[23,25,26,29,32] One of these included males only.[25] People with bipolar disorder[28] and chronic delusion[31] were additionally included in two studies, and one study focused on schizophrenia or schizoaffective disorder depressed type.[34] Two studies included people with and without mental illness, with one specifying the illness as schizophrenia or bipolar disorder,[10] and the other basing it on a self-report of having any mental disorder.[30] Two studies included inpatients of psychiatric facilities. One included patients meeting Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV for schizophrenia or schizoaffective disorders only,[23] while the other included those with diagnoses of mood disorders, schizophrenia and related psychosis, or other.[22]

People with post-traumatic stress disorder were the focus of one study,[24] while the remaining three studies were less specific. One included people with any psychotic disorder based on the Mini International Neuropsychiatric Interview,[33] and the other included anyone with a primary mental illness diagnosis.[27] This last study ultimately ended up including 64/111 (58%) with depression, 14/111(13%) with bipolar disorder, 7/111(6%) with psychosis, 24/111(22%) with psychosis and depression and 2/111(2%) with eating disorders.

All studies required participants to be smokers, but the definition varied. Most commonly, studies required smoking at least 10 cigarettes per day,[24,25,31] with three additionally requiring an expired carbon monoxide (CO) concentration of at least 9[32,34] or 10[26] parts per million. Two required smoking at least 15 cigarettes per day,[28,33] and another two required a self-report of being a current or occasional smoker.[22,23] Other studies implicitly restricted to smokers by recruiting from a tobacco specialist clinic,[27] including those prescribed cessation medication[29] or did not specify.[10,30] In addition to being smokers, almost half of the clinical studies (n=6) only included patients with an expressed desire to quit or reduce their smoking.[24,25,30-32,34]

There were several common exclusion criteria. Eight studies required having a clinically stable disorder,[23-26,31-34] for example, no changes to psychopharmacological maintenance treatment in the six months before the study.[31] People with other substance dependencies were also typically excluded,[24-26,30-32,34] as were those with suicidal ideations or high suicide risk,[25,26,28,31-34] for example, one study stated that participants could not have had any hospitalizations for suicidal ideation in the preceding year.[32]

Guidelines

The guideline's target population was adults aged 18 or older with schizophrenia or psychosis, as well as those involved in decisions concerning their care.[35]

Interventions and Comparators

Systematic reviews

Two systematic reviews included any smoking cessation intervention and comparison.[16,17] The others were more specific. Two reviews included studies where the intervention was

varenicline only,[18,19] of which one included placebo comparisons[19] and the other included placebo or other (unspecified) pharmacotherapy interventions.[18] The third review included nicotine replacement therapy, bupropion and varenicline alone, or in combination, with or without psychological support, compared to placebo or each other.[8] The fourth review included bupropion, alone or in combination with other interventions, with placebo comparators.[6] The remaining two systematic reviews included any pharmacological or non-pharmacological intervention alone or in combination, compared to each other, placebo, or usual care (which was not defined),[20,21] with one also adding no intervention as a comparator.[21]

Clinical studies

Three studies, all randomized, evaluated nicotine replacement therapy (NRT).[22-24] Of these, one compared a two-week supply of an unspecified form of NRT combined with motivational interview, nightly phone calls, an offer for a 12 week additional NRT supply, referral to quit service and smoking cessation groups, to treatment as usual which could consist of advice, NRT for three days and/or a smoking care plan.[22] The second study compared high dose transdermal nicotine patch (31.2mg) to a low-dose patch (20.8mg). Both groups received group psycho-education sessions.[23] The last study using an NRT intervention gave the intervention group two weeks of active nicotine patch loading (21mg) and the comparator was a placebo patch. Both groups also received individual cognitive behavioral therapy sessions.[24]

The standard dose for varenicline across six of seven studies with this intervention was 0.5 mg/day for 3 days, 0.5 mg/day for 4 days, then 1 mg twice daily until end of follow up at 11 weeks[28,31-34] or eight weeks.[26] The remaining study randomized to maintenance treatment among abstinent smokers, providing only 1.0mg twice daily up to 24 weeks.[10] In the randomized studies, the comparator was identical placebo.[10,26] The comparator groups among the non-randomized studies included NRT patch (14, 21, 28 or 35 mg),[28] NRT of variable dose/preparation,[27] or consisted of the same people observed before and after the intervention.[31-34] All studies included some form of behavioral support sessions, usually in group format, that was administered to both treatment and comparator groups.

Two studies' intervention was bupropion combined with forms of NRT.[25,30] The first was an open-label, randomized study where buproprion was administered in combination with nicotine patch and lozenge with some receiving home visits from investigators to provide support, while the comparator group was treatment as usual consisting of a single first-line medication of either nicotine patch, bupropion or varenicline with group cognitive behavioural therapy sessions.[25] The other bupropion study was non-randomized with three treatment arms consisting of nicotine patch plus either bupropion, gum or nortriptyline, while the comparator group received only the nicotine patch. All groups also received group cognitive behavioural therapy sessions.[30]

The final (non-randomized) study had varenicline, NRT (unspecified form) and bupropion treatment groups, and compared the latter two to the varenicline group.[29]

Guidelines

The guideline considered bupropion, varenicline and transdermal nicotine patch.[35]

Outcomes

Systematic reviews

One systematic review did not specify outcomes,[17] and one specified, 'some smoking-related outcome variable was measured [self-reported smoking, breath carbon monoxide (CO), etc]." (pg 181)[16] The rest of the reviews included smoking abstinence or cessation as the primary outcome, with one specifically requiring biochemically verified self-report of cessation.[21] Four systematic reviews considered reduction in smoking[6,18,20,21] and five stated psychiatric outcomes including mental state,[20,21] positive, negative and depressive symptoms,[6,19] psychiatric adverse events,[18] or discontinuation due to psychiatric events.[8] All studies but two[16,17] collected information on adverse events in general.

Clinical studies

The clinical studies generally measured similar smoking cessation and reduction outcomes. The most common criteria for smoking cessation was 7-day point prevalence abstinence, measured in seven studies[22-25,28,30,32] while end of study abstinence was measured in three studies[27,31,34] and weeks of continuous abstinence was measured in three studies.[10,22,32] Thirty-day abstinence was measured in one study,[24] and reduction in smoking was measured in eight studies.[22,23,23,25,26,26,28,33]

Nicotine dependence and withdrawal symptoms were also commonly measured. The Fagerstrom Test for Nicotine Dependence (FTND) was most common for this outcome.[22,23,25,28,33] One study used a self-complete diary to assess smoking craving,[24] while another used a tobacco withdrawal symptoms scale.[27] Other scales used to assess dependence and/or withdrawal included the Glover-Nilsson Smoking Behavioural Questionnare,[28] the Minnesota Nicotine Withdrawal Scale (MNWS),[26,33] the Wisconsin Smoking Withdrawal Scale (WSWS),[25,32,34] the Brief Questionnaire of Smoking Urge[26] and the Modified Cigarette Evaluation Questionnaire (mCEQ).[26]

Fifteen different scales were used to measure psychiatric symptoms and/or safety across seven studies assessing these.[23,25,26,29,32-34] Most commonly, the Scale for Assessment of Negative Symptoms (SANS),[25,26,32,34] the Brief Psychiatric Rating Scale (BPRS),[25,32-34] the Simpson-Angus Rating Scale (SARS),[23,26] and the Positive and Negative Syndrome Scale (PANSS) were used.[23,26] Two studies assessed depressive symptoms using the Hamilton Rating Scale for Depression (HADS),[26] two used the Calgary Depression Scale for Schizophrenia (CDSS).[32,34] and one used the Beck Depression Inventory (BDI).[25,33] One study measured suicidal attempts/behaviours defined through International Classification of Disease (ICD) and E-codes.[29] Other scales used included the Columbia- Suicide Severity Rating Scale (C-SSRS),[25,33] the Abnormal Involuntary Movement Scale (AIMS),[25] the Young Mania rating scale,[33] the Kessler Psychological Distress Scale,[22] the Barnes Akathisia Scale[26] and the Clinical Global Impression (CGI) scale.[25,26]

Guidelines

The guideline did not state specific outcomes of interest.[35]

Summary of Critical Appraisal

Details of the appraisal of individual studies are provided in Appendix 3.

Systematic reviews

All the systematic reviews included at least two databases in their search, though one study stated Medline and PubMed as separate databases which was unclear as Pubmed is an interface for Medline.[16] Two reviews used a limited number of key words for the search, and did not provide details on the included studies or on methods such as screening procedures, or consider study quality or publication bias.[16,17] One of these also conducted some form of meta-analysis that was not described or interpretable.[17]

The remaining six systematic reviews were considered higher quality because they used comprehensive search terms, combined estimates using appropriate statistical methods such as random effects models, and assessed study quality using a study-design checklist,[6] Grading of Recommendations Assessment, Development and Evaluation (GRADE)[8] or the Cochrane Risk of Bias tool.[18-21] Publication bias was planned to be assessed using funnel plots in three studies,[19-21] though two of these ultimately found too few studies to do so.[20,21] The remaining study did not find evidence of publication bias.[19]

Of the five systematic reviews considered higher quality, two did not report their findings regarding study bias despite stating that it was assessed,[8,19] and only one study pointed to an *a priori* review protocol.[20] Two studies were limited to English language and one only involved two abstract screeners for 10% of titles/abstracts rather than all titles and abstracts.[21] Where estimates were combined via meta-analysis, heterogeneity was generally found to be about 0% using I^2 for primary outcomes except one which had an I^2 of 94%, though they conducted sensitivity analysis to explore this.[19]

Clinical Studies

One of the four blinded, randomized studies[10,22-24] provided enough description to judge that allocation concealment was likely successful.[22] There was a similar lack of detail on blinding or randomization procedures in those studies claiming to have done so, though balanced baseline characteristics suggest randomization was adequate and the lack of description of blinding is primarily a concern in the one study without an identical comparator.[22] This study had ill-defined treatment and control interventions that consisted of multiple components that may or may not have been given to all participants.[22] One of the randomized controlled trials was open-label, which may subject the findings to bias induced by knowing the treatment group.[25] This study also had an ill-defined comparator group, as some participants (n=4) received combined nicotine patch, bupropion and varenicline instead of a single medication as was initially specified.

The non-randomized studies were limited by their study design, in that their lacks inherent means (usually achieved by randomization) to balance potentially confounding characteristics that could influence the effect estimates. In place of randomization it would have been important for non-randomized studies[27-34] to consider other participant characteristics that could explain their results and/or use appropriate statistical methods. Three studies adjusted for several potential confounders, such as age, sex, indicators of general health status and baseline smoking profiles,[27,29,30] while one accounted for within-person clustering of standard errors while adjusting for age started smoking.[32] The remaining studies were either unclear or did not undertake an analysis that could minimize the biases induced by lack of randomization.[28,31,33,34] In one of these, the sample size would have been too low for any sophisticated analysis (n=14),[33] and one did have balanced baseline characteristics despite no randomization.[28]

Generalizability of several studies' findings may be limited due to use of a select population based on the study's setting and/or recruitment procedures. Two studies used single psychiatric hospitals,[22,23] one used a specialist tobacco clinic,[27] and two others recruited through flyers and advertising[24,25] with unusually high, and potentially coercive, participant compensation in one ($650).[24] Studies that recruited from multiple sites[10,31,32] or administrative data[29] were thought to be more generalizable. Two studies lacked enough detail to assess generalizability.[26,28]

There were other issues worth mentioning across the studies. First, there was lack of statistical power across several studies. Four studies had a power calculation and were found to be adequately powered[27,29,32] while three[10,23,30] are potentially adequately powered with sample sizes of n=184,[23] n=267,[30] and n=1272,[10] and one potentially underpowered (n=60),[26] though the latter four studies did not mention power calculations. Six studies acknowledged that they may be underpowered,[22,24,25,28,31,33] one of which included 14 participants.[33] Second, there was a lack of clarity in the presentation of results, for example, some studies provided no results tables or summarized form of results,[26,31,34] and some contained post-hoc analyses that were unexplained.[24,32,34]

A strength across studies was the consistent use of biochemically-verified smoking abstinence through parts per million of expired carbon monoxide, except in one study which relied on self-report 7-day point prevalence abstinence.[30] This study also relied on self-report for mental disorder diagnosis to define its population.[30] Another strength was a common strategy to avoid the confounding effect of nicotine withdrawal when assessing adverse events and symptoms by starting treatment before a 'target' quit date.[24,27,27,31,32,34]

Guidelines

The guideline was considered high quality as it was developed based on an explicit review protocol, evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE), and the recommendations were based on an iterative interpretation of evidence by the Guideline Development Group which involved a large range of stakeholders. There was a detailed description of the search and development methods. The only limitation was that external validation was unclear.[35]

Summary of Findings

Details of the findings of individual studies are provided in Appendix 4.

What is the clinical evidence regarding the effectiveness of smoking cessation interventions for patients with severe mental illnesses?

Systematic reviews

The first review found evidence that NRT with psychosocial treatment can help reduce smoking, increase quit rates or maintain abstinence with cessation rates ranging from 23.1% to 66%, while bupropion cessation rates ranged from zero to 66% and did not seem to foster maintenance after abstinence was achieved. Depression or schizophrenic symptoms were not found to worsen.[16] One other review found that the differences between groups in post-treatment proportions of abstinence ranging from 0.12 to 1.0 with NRT, though these were not described in sufficient detail to interpret.[17] The last study attempting to study NRT (in the form of transdermal nicotine patch) could not conclude anything due to small sample sizes and few trials.[20]

Four of five meta-analyses comparing varenicline to placebo found a significantly higher likelihood of abstinence or smoking cessation in the varenicline group.[8,18,20,21] The remaining study did not find a difference (relative risk [RR] = 0.79, 95% confidence interval [CI] 0.58 to 1.08), though it did find that varenicline was associated with increased nausea (RR = 1.79 [95% CI 1.20 to 2.67]). Other studies measuring psychiatric outcomes did not find a difference in side effects including suicidal ideation or depression.[18-21] When comparing varenicline to bupropion, one study found a 'higher probability' that bupropion outranks varenicline, though the conclusion was not firm.[8]

The findings were similar when comparing bupropion to placebo. There were significant higher likelihood of smoking abstinence and/or cessation in three reviews,[6,8,20] and one review found mean differences in proportion abstinent ranging from 0 to 0.77.[17] One review additionally found a significant change in cigarettes per day (mean difference = -10.77 [95% CI -16.52 to -5.01]) and two found significantly lowered expired CO at end of treatment (mean difference = -6.80 [95% CI -10.79 to -2.81],[20] -6.84ppm [95% CI -11.11 to -2.56][6]). There were no differences in mental state outcomes.[6,20] When comparing bupropion to any intervention, there were also significant differences in medium (3.5 months) and long term (11.75 months) quit rates (RR = 2.93 [95% CI 1.61 to 5.34] and RR = 3.04 [95% CI 1.10 to 8.42], respectively), but not short-term. Similarly, there were no significant differences in changes in psychiatric symptoms, except one study found significant worsening of cognitive score in bupropion intervention group compared to placebo.[21] Bupropion plus NRT compared to placebo plus NRT was not found to increase smoking cessation rates (odds ratio [OR] = 4.13 [95% CI 0.92 to 18.47]).[8]

Clinical Studies

The three randomized studies evaluating nicotine replacement therapy (NRT)[22-24] had different conclusions. One study did not find a difference in time to relapse or 6-week or 6-month abstinence among those randomized to active versus placebo NRT patches in a PTSD population.[24] The remaining two studies were among inpatients. One also failed to find any difference in 7-day point prevalence abstinence, daily number of cigarettes, expired CO, nicotine craving or other symptom scales.[23] The other inpatient study of NRT did find an almost three-fold increase in the likelihood of having a quit attempt (OR = 2.89 [95% CI 1.43 to 5.98]) and in the likelihood of reducing cigarettes smoked per day by 50% (OR = 5.90 [95% CI 2.89 to 15.25]), and a decrease in nicotine dependence (mean difference on FTND = −1.6 [95% CI −2.3 to −0.8]), though no effect on 7-day point prevalence abstinence at six months.[22] It is important to note this last study had a more complex intervention that provided additional support to participants. There was limited reporting of adverse events or psychiatric safety outcomes, but in the study of high versus low dose NRT inpatients, five participants discontinued due to unspecified side effects.[23] No group differences in psychological distress was found in the other inpatient study.[22]

The two randomized studies comparing varenicline to placebo both found significant effects on smoking abstinence. At week eight, the varenicline group had significantly lower expired CO compared to placebo (P=0.019), though there were no significant differences in measures of withdrawal, number of cigarettes smoked, or smoking urge.[26] The other study using varenicline versus placebo for maintenance therapy found their schizophrenia/bipolar disorder (SBD) population had significantly lower abstinence rates overall compared to the non-SBD population (OR = 0.27, [95% CI 0.13 to 0.56]), except within the varenicline-assigned group, there was no difference (OR = 1.68, [95% C: 0.53 to 5.32]).[10] Similarly, among varenicline-assigned participants, there were no significant differences between SBD and others in the rate of 7-day point-prevalence abstinences, though odds of

achieving abstinence were lower for SBD patients in the placebo group compared to others (OR = 0.87; *P* = 0.011).[10] Three participants with adverse events (3/60) including nausea (1/30 in each group), headache (1/30 in the varenicline group), and two participants with aggravated psychotic symptoms between weeks 2 and 4 withdrew from one of the trials.[26]

Two non-randomized studies of varenicline against NRT had opposing results. One study did not find any difference in 7-day point prevalence abstinence or in number attaining > 50% reduction in number of cigarettes per day, expired CO level, or nicotine dependence, against transdermal nicotine patch.[28] The other did find an increased likelihood of continuous 2-week abstinence in the varenicline group at the eight week follow up in the total and mental illness population, though the effect was stronger in the mental illness population (OR = 2.88 [95% CI 1.08 to 7.63] in mental illness sample vs OR = 1.70 [95% CI 1.09 to 2.67] in total sample).[27]

Both non-randomized studies found higher rates of adverse events in the varenicline versus NRT groups. One study found more frequent nausea, disturbed sleep, vivid dreams, drowsiness, constipation, headache, dyspepsia, dry mouth, bad taste, low mood, diarrhea and disorientation in the varenicline group, and seven patients switched from varenicline to NRT due to unspecified adverse symptoms. The rates of adverse events were not different in those with and without mental illness.[27] The other study found significant weight gain in both groups, and 10% more participants reporting at least one adverse event in the varenicline group (21/36 [58.3%] in NRT versus 27/39 [69.2%] in the varenicline group), most commonly abnormal/vivid dreams (n=9 and n=4, respectively), constipation (n=5 and n=9, respectively), and nausea/vomiting in the varenicline group only [n=12]). Four (10.2%) switched treatment groups due to adverse events and three (7.8%) reduced their varenicline dose.[28]

The cohort studies that compared outcomes pre and post treatment with varenicline were generally positive. A significant decrease in cigarettes per day at six months (Mean difference [B] = 13.61 [95% CI 6.58 to 20.75])[33] and significant increase in 7-day point prevalence abstinence at 12 weeks were observed (B= 0.34, standard error [SE] = 0.03, *P* < 0.01).[32] The latter study also found significant declines in the urge to smoke and WSWS scores.[32] Two studies found that 41.1% (n=37) and 41.3% were abstinent at the end of the 12-week follow up.[31,34] One of these further found declines in withdrawal scores among those who attained abstinence, but not among non-abstinent completers or those who dropped out,[34] while the other had less conclusive findings regarding nicotine dependence and withdrawal symptoms. Two studies measuring expired CO level had opposite findings, though the one without significant results measured this outcome at six months,[33] while the other measured it at twelve weeks (B =−0.03 [SE = 0.01], *P* < 0.01).[32] Gastrointestinal issues such as nausea were found in all varenicline non-randomized studies. Sleep disturbance or abnormal dreams was also one of the most common adverse events in two studies,[31,34] while suicidal ideation or psychiatric issues resulted in discontinuation in n=1/14,[33] n=1/90[31] and n=1/110[32] participants. Two studies reported a significant decrease in symptom scores over time as measured by CDSS,[32,34] and BPRS-Psychosis scale.[32] There were no significant changes observed across the other symptom scales in any of the studies.

The two bupropion plus NRT studies also had positive findings. In one study, the two bupropion treatment plus NRT groups (with and without home visits) had significantly greater reduction in cigarettes per day and expired CO level compared to treatment as usual with any first-line medication. The treatment combined with home visits was

associated with significant differences in FTND scores at 6 months (change of -2.2 vs -4.2, $P < 0.05$) and in 7-day point prevalence abstinence rates ($\chi 2(1) = 4.8$, $P = 0.03$), compared to treatment as usual.[25] The other bupropion study found a slightly increased likelihood of reporting 7-day abstinence when combined with nicotine patch, compared to nicotine patch alone (OR = 2.00 [95% CI 1.14 to 3.50]), and in nicotine patch plus gum compared to nicotine patch alone (OR = 2.10 [95% CI 1.04, 4.23]) though both the confidence intervals' lower bounds approached the null value of one. No effect was observed for treatment retention, or for any outcome among participants without mental disorders.[30]

In the open label bupropion study,[25] psychiatric and symptom measures were similarly not different across groups as measured by six scales, though 27%, 30% and 46% reported adverse events in treatment with home visits, treatment without home visits and treatment as usual groups respectively, most commonly insomnia (n = 4/34), with vivid dreams (n = 2/34), nausea (n = 2/34), rash (n = 2/34), agitation (n = 1/34).

The final study did not observe a difference in suicide attempts/behaviours, as per ICD-9 classification codes, between participants prescribed NRT or bupropion compared to varenicline after 12 months follow up (hazard ratio [HR] = 0.81 [95% CI 0.51 to 1.28] and HR = 0.37 [95% CI 0.05 to 2.70], respectively).[29]

What are the evidence-based guidelines regarding smoking cessation interventions for patients with severe mental illnesses?

To help stop or reduce smoking, the NICE guidelines recommended considering NRT or varenicline for people with psychosis or schizophrenia, and bupropion for people with schizophrenia. They also suggest warning patients of an increased risk of neuropsychiatric symptoms and to monitor patients more closely in the first 2-3 weeks. NRT can be offered to inpatients who do not express a desire to stop smoking.[35]

Limitations

Limitations of this review include the poor quality studies, and the small sample sizes which are evident from the generally large confidence intervals found in several studies. The included systematic reviews found similar quality issues of primary studies, commenting on the small sample sizes,[6,18] high/unclear risk of bias due to poor reporting,[6,8,21] and inter-study variability,[17,18] which make their conclusions weaker.

There was also inconsistency across the clinical studies in terms of their definitions of 'smoker', the interventions and comparators, making generalizations about which treatment components are responsible for the observed effects difficult. Most studies focused on people with schizophrenia or schizoaffective disorder, so generalizability beyond this population may be limited, and the longest follow up duration on treatment was six months, except in one study that did not find an increase in suicidal attempts/behaviours after one year.[29]

Conclusions and Implications for Decision or Policy Making

While concerns about safety may prevent pharmacological options from being used more often among people with severe illness, the current review did not find evidence for an increased risk of adverse events compared to the general population, or worsening of psychiatric symptoms when using NRT, varenicline or bupropion with people with severe mental illness.

All three interventions were found to improve smoking cessation rates compared to placebo or no treatment, varenicline and bupropion may be more effective than NRT, and additional psychosocial support may enhance success. Nausea and sleep disturbances were common when using varenicline, but peaked and declined with time. Sustained effects beyond the treatment period were not generally measured, nor were varying dosages except for one study which found higher NRT dose did not improve outcomes.[23]

In general, the quality of studies was low and sample sizes small, suggesting the need for better reporting across these studies and more adequately powered analyses.

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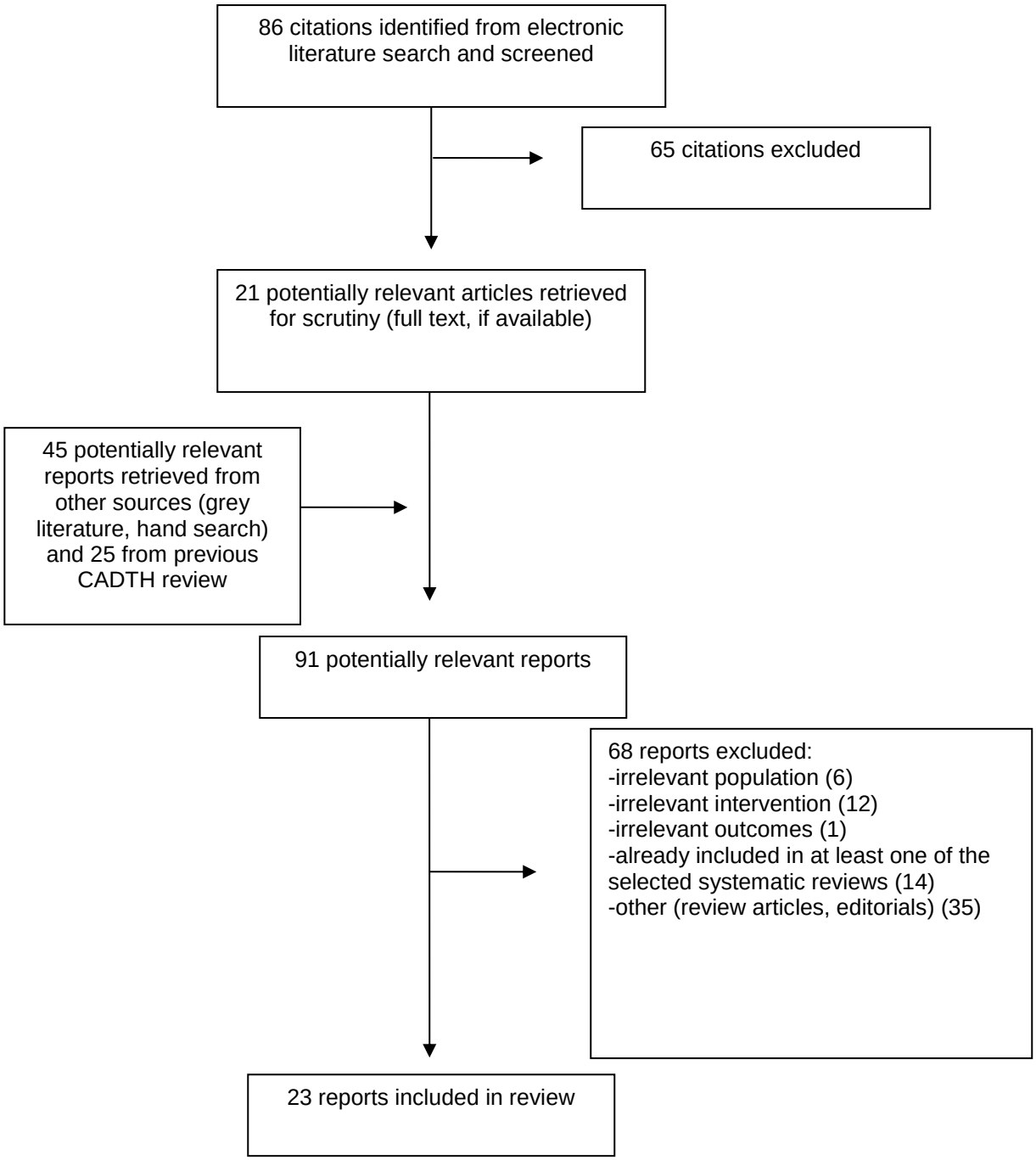
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 1: Characteristics of Included Systematic Reviews

First Author, Publication Year	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes
Bennett, 2013[16]	-Types of studies not described -29 studies included, of which 22 studies included pharmacological intervention (NRT = 2, bupropion = 11, varenicline = 2, NRT + psychosocial intervention = 5, bupropion + psychosocial intervention = 2)	50% or more individuals in sample with schizophrenia spectrum diagnosis	"Some individual or group intervention for smoking cessation was provided" (pg 181)	None stated	"Some smoking-related outcome variable was measured [self-reported smoking, breath carbon monoxide (CO), etc]." (pg 181)
Ferron, 2009[17]	13 prospective studies that did not use a single-subject design	People who smoke, with schizophrenia spectrum disorders	None stated ("an intervention for smoking cessation", pg 66)	None stated	Eliminating or reducing smoking
Kishi, 2015[19]	-Double-blinded RCTs only -Seven doubled-blind, randomized, placebo-controlled trials included comparing varenicline to placebo selected	Individuals with schizophrenia, schizoaffective disorder, schizophreniform disorder or delusional disorder	Varenicline	Placebo	-Smoking abstinence rate -Positive, negative, and depressive symptoms, discontinuation rate, and individual side effects.
Peckham, 2017[21]	RCTs only (28 studies included in total, of which 16 focused on pharmacological interventions including n=9 burpoprion, n=6	Aged 18 or older and ICD or DSM IV diagnosis of schizophrenia or other psychotic disorders, bipolar disorder and	Behavioural or pharmacological (any products licensed for smoking cessation) as monotherapy or	Each other, placebo, usual care or no intervention	-Biochemically-verified self-reported smoking cessation -Smoking reduction, change in body weight, change in

First Author, Publication Year	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes
	varenicline, n=1 NRT)	depression with psychotic features, but not personality disorder, severe anxiety disorder, PTSD, major depression or autism.	in combination		psychiatric symptoms (any validated scale) -Adverse events
Roberts, 2016[8]	-Included RCTs only -17 studies representing 14 RCTs were included (bupropion to placebo = 6, varenicline to placebo = 5, bupropion to varenicline and placebo = 1, bupropion plus NRT to placebo plus NRT = 2)	Adults who currently smoke with motivation to quit or reduce smoking, with severe mental illness including schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder or depressive psychoses	NRT, bupropion or varenicline alone or in combination, with or without psychological support	Placebo or other intervention	-Sustained smoking cessation (6 months or longest reported time point) -7-day point prevalence abstinence rate -Discontinuation due to adverse events
Tsoi, 2010[6]	RCTs only (included 21 reports of 7 trials)	Smokers with a current diagnosis of schizophrenia according to either the ICD–10 or the DSM–IV were included.	Bupropion, including bupropion combined with other pharmacological or non-pharmacological interventions	Placebo	-Abstinence -Change in severity of smoking dependence -Change in mental state (positive, negative and depressive symptoms using validated tools) -Adverse events
Tsoi, 2013[20]	34 randomised trials, of which 10 focused on pharmacological interventions (n=7 bupropion to placebo, n=2 varenicline to	Adult smokers with ICD or DSM diagnosis of schizophrenia or schizoaffective disorder -4 trials recruited	Pharmacological or non-pharmacological interventions (alone or in combination) for smoking	Another pharmacological or non-pharmacological intervention, placebo or usual care	-Smoking abstinence at longest follow-up -Change in mental state -Smoking abstinence at end of intervention

First Author, Publication Year	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes
	placebo, n=1 contingent reinforcement vs NRT)	inpatients only	cessation/reduction.		-Reduction of smoking behaviour or dependence -Other adverse events
Wu, 2016[18]	Included RCTs and quasi-randomized controlled trials (8 RCT studies comparing varenicline to placebo selected)	Adults (over age 18) with any type of severe mental illness	Varenicline	Placebo or other pharmacotherapy intervention	Smoking cessation, reduction in number of cigarettes per day and safety (number of psychiatric adverse events)

RCT = randomized controlled trial; NRT = nicotine replacement therapy; ICD = International Classification of Disease; DSM = Diagnostic and Statistical Manual of Mental Disorders

Table 2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Brody, 2017, U.S. Combination extended smoking cessation treatment plus home visits for smokers with schizophrenia: a randomized controlled trial[25]	Open label RCT	Adult male smokers with DSM IV criteria diagnosis of schizophrenia who smoke 10 to wu cigarettes per day and a desire for cessation treatment living independently or in a supervised arrangement.	Bupropion plus nicotine patch, nicotine lozenge, + group CBT (with and without home visits by study investigator)	Treatment as usual (group CBT plus single first-line smoking cessation medication)	-7-day point prevalence abstinence -Number of cigarettes -Dependence, withdrawal, urge (FTND, WSWS) -Safety measures: BPRS, SANS, CGI, BDI, C-SSRS, AIMS
Castle, 2012, Australia, Varenicline plus healthy lifestyle intervention for smoking cessation in psychotic disorders[33]	Pre/post study	Patients at least 18 years old with psychotic disorder based in Mini International Neuropsychiatric Interview, with stable medication for last 3 months and smoking	Varenicline 0.5 mg/d for days 1 to 3; 1 mg/d for days 4 to 7; and 2 mg/d days 8 to 84 + Healthy Lifestyles program	None	-Expired CO -Opiate Treatment Index -Dependence, withdrawal, urge (FTND, MNWS) -Psychiatric symptoms

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
		at least 15 cigarettes per day.			(BPRS, BDI, Young Mania Rating Scale) -Safety check using C-SSRS
Cather, 2017, U.S., Improved depressive symptoms in adults with schizophrenia during a smoking cessation attempt with varenicline and behavioral therapy[34]	Pre/post study	Participants with schizophrenia or schizoaffective disorder, depressed type (SSD), aged 18 to 70 years, reported smoking 10 cigarettes per day for at least the past year with expired CO concentration >= ppm, taking stable dose of antipsychotic medication for 30+ days, with a desire to quit smoking.	Varenicline 0.5 mg daily for three days, 0.5 mg twice daily for four days, and 1 mg twice daily for 11 weeks + group CBT tailored for smokers with severe mental illness	None	-End-of-study abstinence -Depressive symptoms, withrawal (CDSS, WSWS)
Chen, 2013, Taiwan, A double-blind randomized clinical trial of different doses of transdermal nicotine patch for smoking reduction and cessation in long-term hospitalized schizophrenic patients	Blinded RCT	Patients from chronic wards of psychiatric hospital meeting DSM-IV criteria for schizophrenia or shizoaffective disorders, who were regular smokers.	High dose NRT (31.2mg TNP) for 4 weeks, then 20.8mg for 4 weeks + group psycho-education	Low dose NRT (20.8mg TNP) for 8 weeks + group psycho-education	-Number of cigarettes -7-day smoking abstinence -Expired CO -Dependence (FTND) -Psychiatric symptoms (PANSS, SARS)
Dennis, 2016, US, Supplemental nicotine preloading for smoking cessation in posttraumatic stress disorder: results from a randomized controlled trial[24]	Blinded RCT	Individuals with PTSD (Clinician Administered PTSD Scale) aged 18-70, with a desire to quit smoking and smoking at least 10 cigarettes per day in the past year.	2 weeks active nicotine patch loading (21mg/24 h patch) prior to quit date + individual CBT + six weeks 21mg/24 h patch post-quit and one form of rescue nicotine replacement (e.g. gum)	2 weeks placebo nicotine patch prior to quit date + individual CBT + six weeks placebo patch post-quit	-7-day point prevalence abstinence -Thirty-day smoking abstinence -Diary assessments for smoking frequency and craving, and PTSD symptoms

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Evins, 2017, Multiple. Maintenance pharmacotherapy normalizes the relapse curve in recently abstinent tobacco smokers with schizophrenia and bipolar disorder[10]	Blinded pooled analysis of two RCTs	Participants with and without schizophrenia or bipolar disorder with a 14 or 7 day point prevalence abstinence at week 12 of the initial cessation treatment	Varenicline treatment (1.0mg twice per day) + tapering behavioral support	Identical placebo + tapering behavioral support	-Four-week continuous abstinence rates after 12 weeks of maintenance therapy -Time to first relapse
Garcia-Portilla, 2016, Spain, It is feasible and effective to help patients with severe mental disorders to quit smoking: An ecological pragmatic clinical trial with transdermal nicotine patches and varenicline[28]	Cohort study	Patients with DSM-IV diagnoses of schizophrenia, schizoaffective or bipolar disorder, smoking >= 15 cigarettes/day for at least 1 year without any abstinence periods longer than 1 month, FTND score >=4, expired CO > 9 ppm, aged 18-65	Varenicline 0.5 mg/day for the first 3 days, 0.5 mg twice daily on days 4–7, and 1 mg twice daily for the remaining 11 weeks. (preceded by 4-12 weeks individual motivational therapy)	TNP 24 hour at 14, 21, 28 or 35 mg. (preceded by 4-12 weeks individual motivational therapy)	-7-day point prevalence abstinence -Proportion with >= 50% reduction in number of cigarettes per day in the last week -Dependence, withdrawal, urge (FTND, Glover-Nilsson Smoking Behavioural Questionnaire)
Jeon, 2016, Korea, Adjunctive varenicline treatment for smoking reduction in patients with schizophrenia: a randomized double-blind placebo-controlled trial[26]	Blinded RCT secondary analysis	Aged 18 to 60 years, score 75 or less on PANSS and no medication changes for last 3 months, with DSM-IV diagnosis of schizophrenia receiving antipsychotic medication. 'Smoker' = smoking > 10 cigarettes daily for at least 1 year with expired CO level >10ppm.	Varenicline, 0.5 mg for days 1–3, 0.5 mg twice per day for days 4–7, and 1 mg twice daily for weeks 2–8 + self-help booklet and weekly telephone visits.	Identical placebo + self-help booklet and weekly telephone visits.	-Expired CO -Number of cigarettes -Dependence, withdrawal, urge (MNWS, Brief Questionnaire of Smoking Urge, m-CEQ) -Psychiatric symptom/safety (HADS, PANSS, SANS, SARS, CGI, Barnes Akathisia Scale)

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Loreto, 2017, Brazil, Smoking cessation treatment for patients with mental disorders using CBT and combined pharmacotherapy[30]	Retrospective cohort	Aged 18 to 65, attended health centre staff at least once during treatment protocol, voluntarily participate in the smoking cessation treatment, with a prescription for nicotine patch alone or in combination with another medication.	-Nicotine patch plus bupropion -Nicotine patch plus gum -Nicotine patch plus nortriptyline All interventions included group CBT	Nicotine patch + group CBT	-7-day point prevalence abstinence -Retention
Pachas, 2012, US, Varenicline for smoking cessation in schizophrenia: safety and effectiveness in a 12-week, open-label trial[32]	Pre/post study	Aged 18-70 with DSM-IV-text revision diagnosis of schizophrenia or schizoaffective disorder, smokied >= 10 cigarettes per day, clinically stable (stable antipsychotic medication for >= 1 month), expired CO > 9ppm, with desire to quit smoking. Excluded those with dementia, other substance use disorder in last 6 months and hospitalization for suicidal ideation in past 12 months	Varenicline 0.5 mg/day for 3 days, 0.5 mg/day for 4 days, then 1 mg twice daily for 11 weeks and weekly, + group CBT based on Freedom From Smoking program	None	-7-day point prevalence abstinence -Weeks of continuous abstinence -Dependence, withdrawal, urge (FTND, WSWS) -Psychiatric symptoms (SANS, CDSS, BPRS)
Raich, 2016, Spain, Safety of varenicline for smoking cessation in psychiatric and addicts patients[31]	Pre/post study	Aged 18 or older with a diagnosis of nicotine dependence, who smoked more than 10 cigarettes/day in the past year with a desire to quit, with psychotic disorder (schizophrenia, schizoaffective disorder or chronic delusion)	Varenicline 0.5 mg per day for 3 days, 0.5 mg twice a day from days 4 to 7, and 1 mg twice a day during the following 11 weeks + initial visit with CBT	None	-End-of-study abstinence

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Stapleton, 2008, UK, Varenicline in the routine treatment of tobacco dependence: a pre–post comparison with nicotine replacement therapy and an evaluation in those with mental illness[27]	Cohort study	No exclusions except pregnant or breastfeeding, trying to conceive, under 18 years old, severe renal function impairment (3) were excluded routinely from 111 (67%) had mental illness with primary diagnosis: 64/111 (58%) depression, 14/111(13%) bipolar disorder, 7/111(6%) h psychosis, 24/111(22%) psychosis and depression and 2/111(2%) eating disorders.	Varenicline (12-week course) plus group support sessions	Variable dose NRT plus group support sessions 1.5 hours (60% nicotine patch, 25% nasal spray, 11% gum or lozenge and 5% inhalator/microtab, + offer of 2nd NRT product to be used in combination)	-End-of-study abstinence -Self-completion tobacco withdrawal symptoms scale
Stockings, 2014, Australia, Impact of a postdischarge smoking cessation intervention for smokers admitted to an inpatient psychiatric facility: a randomized controlled trial[22]	Blinded RCT	Patients of psychiatric facility over 12 months (May 2010-11) who are at least 18 years old and self-reported smoker; diagnoses (reduced to mood disorders, schizophrenia and related psychosis, other)	Treatment as usual + motivational interview and 2-week supply of NRT, nightly phone calls with offer for 12-week additional supply of NRT, referral to quit service, smoking cessation groups	Treatment as usual (any of: brief advice to quit, NRT during admission and for 3 days post-discharge, smoking care plan in discharge summary)	-Continuous abstinence (from date of discharge) -7-day point prevalence abstinence -Prevalence of quit attempts (not smoking for at least 24 hours) -Number of cigarettes -dependence (FTND) -Psychological distress (K10))
Wu, 2017, U.S., Comparison of suicide attempts/behaviors following smoking cessation treatments among schizophrenic smokers[29]	Retrospective cohort	Enrolled in database between 12/13/1995 and 10/31/2011 with ICD-9 code diagnosis of schizophrenia or schizoaffective disorder, above age 18, not prescribed Bupropion for depression in 6 months prior, not	Varenicline NRT Bupropion	Varenicline used as reference	Suicidal Attempts/Behaviors

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
		prescribed other medication on same day as index medication and newly initiated cessation medication			

RCT = randomized controlled trial; NRT = nicotine replacement therapy; TNP = transdermal nicotine patch; CO = carbon monoxide; ppm = parts per million; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders; CBT = cognitive behavioural therapy; FTND = Fagerstrom Test for Nicotine Dependence;MNWS = Minnesota Nicotine Withdrawal Scale; WSWS = Wisconsin Smoking Withdrawal Scale; mCEQ = Modified Cigarette Evaluation Questionnaire; BPRS = Brief Psychiatric Rating Scale; SARS = Simpson-Angus Rating Scale; PANSS = Positive and Negative Syndrom Scale; HADS = amilton Rating Scale for Depression; CDSS = Calgary Depression Scale for Schizophrenia; BDI = Beck Depression Inventory; C-SSRS = Columbia- Suicide Severity Rating Scale; AIMS = Abnormal Involuntary Movement Scale; K10 = Kessler Psychological Distress Scale; CGI = Clinical Global Impression

Table 3: Characteristics of Included Guidelines

Citation	Intended users/Target pop	Intervention and Practice Considered	Outcomes	Evidence collection, selection and synthesis	Evidence Quality and Strength	Recommendations development and Evaluation
NICE[35]	Target population is adults with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis, and intended users are primary, community, secondary, tertiary and other healthcare professionals who make decisions concerning their care	Bupropion, varenicline and transdermal nicotine patch	Any	-Literature search involved 15 databases and based on Cochrane review with a new search to update -Meta-analysis complete where possible	-For bupropion vs placebo, three studies ranked 'moderate' and remaining 4 were low or very low -For varenicline vs placebo, both studies graded 'low' -Nicotine patch study was from a conference paper	Guideline Development Group drafted recommendations based on evidence summaries, with assistance of special advisors

RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[12]

Strengths	Limitations
Bennett[16]	
-Three databases searched (Pubmed, Medline, Psycinfo)	-No dates specified -Limited key words used (only “smoking cessation”, “nicotine dependence” “schizophrenia”, “serious mental illness”, and “smoking treatment outcomes”.) -Research question vague -No critical appraisal or table of study descriptions -No flow chart of study selection or procedures for data extraction or abstract review -Limited to English language
Ferron[17]	
-Hand searching of references	-Only two databases searched (PsychInfo and PubMed) -Limited number of search terms -No flow chart or details on extraction procedures -Research question vague -No risk of publication or study bias assessed -Unclear statistical methods to determine effect sizes
Kishi[19]	
-PubMed, the Cochrane Library databases, and PsycINFO up to 2014 -No language restriction -Hand searched reference lists -Trials identified by two authors -Quality assessed using Cochrane risk of bias assessment -Combined results using random effects model -Reported relative, absolute and measures of impact -Funnel plot to assess publication bias	-Double-blinded RCTs only -Limited databases -Did not report quality findings
Peckham[21]	
-Registered review protocol -Searched 6 databases (MEDLINE (PubMed), EMBASE, PsycINFO, CINAHL, Health Management Information Consortium (HMIC) and	-Limited to English -Did not have 2 independent screeners for all studies (validated in 10% of studies only)

Strengths	Limitations
CENTRAL) -Search strategy adapted from terms developed by Cochrane group -Hand-searched reference lists -2 authors independently decided which studies to include and extracted the data -Cochrane risk of bias tool used to assess study quality -Appropriate statistical methods for meta-analysis -Assessed publication bias risk through funnel plots	
Roberts[8]	
-Embase, Medline, PsychINFO and the Cochrane Central Register of Controlled Trials searched until 2014 -Abstracts assessed by two authors + hand searching for additional citations -Quality assessed using GRADE -Imputation of outcomes for missing participants as continuing smokers -Appropriate methods for meta-analysis, i.e. random effects model for pairwise comparisons, and Bayesian random effects for network linking	-Limited to RCTs and English language studies -No exploration of publication bias and did not report quality findings
Tsoi[6]	
-Included Cochrane Central Register of Controlled Trials of the Cochrane Library, MEDLINE, EMBASE and PsycINFO, as well as unpublished studies, conference abstracts, trial records and reference lists -No date or language restrictions -2 authors independently decided which studies to include and extracted the data -Assessed study quality based on allocation concealment, masking, completeness of follow-up and ITT analysis -Assessment of heterogeneity and appropriate methods for meta-analysis	-Did not use external quality assessment tool -No assessment of publication bias
Tsoi[20]	
-Clear PICO question -A priori protocol -Inclusion of both RCTs and quasi-RCTs -Searched several databases including Cochrane Tobacco Addiction Group Specialised Register, CENTRAL (the Cochrane Central Register of Controlled Trials), MEDLINE, EMBASE, PsycINFO, CINAHL, BIOSIS Previews and Web of Science, in addition to trial registry platforms -No date or language restrictions	-Lack of summary of risk of bias across studies

Strengths	Limitations
-Three authors independent screening and two authors extracted data -Risk of bias assessed using Cochrane methodology, heterogeneity and reporting biases assessed using funnel plots -Appropriate meta-analysis methods	
Wu[18]	
-Searched MEDLINE, EMBASE, PsycINFO, CINAHL and the Cochrane Library in September 2015 -No language restrictions -Hand searched reference lists -Trials identified by two authors -Quality assessed using Cochrane risk of bias assessment -Combined results using random effects model -Report both risk ratio and odds ratio	-Unclear how 'smoker' was defined -No exploration of publication bias

RCT = randomized controlled trial

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black[13]

Strengths	Limitations
Evins[10]	
-Blinded, randomized controlled trial -International patient population improves generalizability -Appropriate statistical analysis with covariates including gender, race, age, and severity of nicotine dependence -Exploration of missing data impact using imputation models, and appropriate combining of imputed datasets -Large sample size (n=1293) -Sensitivity analysis to assess the impact of decisions on missing data handling and baseline differences	-Lack of detail on blinding or allocation concealment procedures, or inclusion and exclusion criteria -No table to compare characteristics of placebo versus treatment groups, or to present regression results -Present odds ratios despite using survival analysis (which is usually presented as hazard ratios)
Chen[23]	
-Blinded, randomized trial -Appropriate statistical analysis -ITT analysis	-Unclear definition of smoker -No detail on allocation concealment, blinding, randomization or recruitment procedures

Strengths	Limitations
-Successful randomization as balanced baseline characteristics achieved	-Public psychiatric hospital setting only -Lack of power calculation despite conducting pilot study, however sample size relative large (n=184) -Did not provide exact p-values
Dennis[24]	
-Blinded, randomized trial -Blinding achieved through making the list unavailable to study coordinators or investigators -Appropriate multi-level statistical modeling to account for repeat measures on each person -Baseline characteristics balanced	-Recruitment through flyers/letters could induce selection bias -High compensation ($650) potentially coercive -Unclear whether rescue NRT (e.g. gum) was also given in placebo format, or how this was used -Lack of detail on allocation concealment, study setting or power calculation -Post-hoc statistical analysis without mention in methods -Unclear mixing of ITT and as-treated analysis -No PRISMA diagram
Stockings[22]	
-Blinded, randomized trial -Evidence of successful allocation concealment from all project and clinical staff and follow up interviewers -Patients approached upon admission to determine eligibility, minimizing selection bias -Successful randomization except higher occurrence of bipolar disorders as primary diagnosis (mean 9.9 in control vs 18.3 in intervention group) -ITT analysis using generalized mixed modelling to examine differences over time, or odds ratios otherwise	-Single site may limit generalizability -Treatment and control interventions not well-defined
Jeon[26]	
-Blinded, randomized trial -Successful blinding through identical capsules -Balanced baseline characteristics achieved, though slightly elevated average daily neuroleptic dose in placebo group (mean = 624.17mg versus 457.93 mg in varenicline group)	-No description of randomization procedures -Recruitment procedures not described -Statistical analysis questionable due to use of repeated-measures ANOVA for time trajectories, as only results in a p-value -Unclear presentation of results, and difficult to decipher the specific contrasts

Strengths	Limitations
Garcia-Portilla[28]	
-Measured baseline characteristics were generally balanced despite no randomization -Statistical analysis was appropriate except if there were unmeasured, unbalanced characteristics predicting the outcome, which should have been adjusted for -'Real world' setting	-Non-randomized; treatment given according to patient and provider preferences, and somatic comorbidities (which can also be a consequence of the treatment, so adverse events may be underestimated) -No details on recruitment procedures so generalizability unclear -Open label -Comparison not well-defined as nicotine patches were given at several different doses without stratification -Last observation carried forward (LOCF) method for missing data may not be appropriate if participant relapses after loss to follow up -4 patients changed from treatment to comparator due to adverse event (elevated liver enzymes, nausea) or at their own request -Did not adjust for site clustering in statistical analysis
Stapleton[27]	
-Power calculation demonstrates sufficiently powered study -Baseline characteristics across groups were similar -Appropriate statistical model, adjusting for sex, race, education, age, on benefits, other health disorder, tobacco smoking severity, though unclear accounting for correlation within individuals -Large sample size overall (n=404)	-Recruitment for specialist tobacco clinic may limit generalizability -Mental illness participants not specifically recruited, and only a secondary analysis -Treatment not randomized, based on patient preferences -Not feasible to compare adverse event occurrence because of low sample sizes in mental illness group across individual symptoms
Brody[25]	
-Balanced randomization achieved, except treatment group with home visits had higher average scores on Brief Psychiatric rating Scale (49.4 versus 45.3 and 47.1 in TAU and treatment group with no home visits, respectively) and Beck Depression Inventory (14.2 versus 10.2 and 10.3 in TAU and treatment group with no home visits, respectively) -Generalized linear mixed model used to estimate time trajectories of cigarettes per day, while controlling for within-person effects	-Pilot study so potentially underpowered -Recruited via flyer advertisements from the smoking and schizophrenia treatment programs = select population -Small sample size (n=34) reduces interpretability of statistical model results, especially due to the complexity of the model choice (including an unstructured trajectory over time) -Possibility of spill-over effects as some participant in TAU (n=4) received all three medications as well
Castle[33]	
-Appropriate statistical analysis (t-test) given the low sample size	-No objective measure of smoking -Small sample size (n=14)

Strengths	Limitations
	-No randomization or control, so cannot rule out other factors explaining the observed differences -No important characteristics of individuals reported
Cather[34]	
-Lead-in period of one month prior to the quit date used to distinguish adverse events associated with pharmacotherapy from nicotine withdrawal	-Not possible to differentiate effect of medication versus behavioural therapy on the outcomes, though stronger case for medication effect as effect is seen immediately after initiation -No confidence intervals or results table from statistical models available, as well as several comparisons that were not stated a priori, limiting interpretability of the results -Unclear design: authors call the study a 'trial', but design would suggest this is more like a pre/post study as the comparison is the subjects' own baseline score; if a case-crossover design, statistical analysis was not typical of matched study (i.e. conditional logistic) -Unclear whether model was adjusted for covariates -Non-randomized study with unclear comparator group
Raich[31]	
-Multi-centre study: 11 specialized tobacco addiction units of the Substance Abuse Treatment Network of Catalonia -'Real life' setting may improve generalizability -High drop-out rate (53/90) = 59%	-May be underpowered because could only recruit 90 patients versus 129 calculated as required -Treatment not randomized -No comparator group -Statistical analysis did not adjust for any other factors that may have changed - no parametric model -Unclear presentation of results; no table and single report that all were abstinent
Loreto[30]	
-Primary outcomes not stated a priori -Power calculation demonstrated sufficient power -Adjusted p-values for multiple testing -Strong statistical analysis account for correlation between repeat observations and adjusted for baseline demographic descriptors, biological descriptors, and indices of nicotine dependence -Investigated confounding potential of retention, though arguably unnecessary for ITT analysis -Missing measurements considered smokers	-Multi-centre study (major hospitals and universities in partnership with local mental health centers) -Unclear how treatment was assigned, randomization or recruitment procedures -No comparison group except self, so cannot rule out other explanatory factors

Strengths	Limitations
Wu[29]	
-Use of large EMR database with over 7.4 million patients, and large sample size meeting eligibility criteria (n=3925) -Appropriate use of Cox regression model to analyse time to suicide/censoring -Adjusted for mostly appropriate covariates (age, race, gender, region, BMI, payment type (government or non-government insurance), specialty group, comorbidity index, and severity of mental disorder -Representative population	-Use of prescription as exposure does not mean patients filled prescription -Censoring of patients who switched smoking cessation medication could exclude those at highest risk of suicide (bias effect towards the null) -Adjusting for previous suicide behaviors/attempts or depression may induce confounding if there are common causes of the initial suicide attempt/behaviour and the observed one -Potential for misclassification using ICD-9 codes for suicidal/self-injurious behavior -Non-randomized study with no comparator group -Not possible to discern whether participants actually smoked or the actual indication for the medication -Lack of description of missing data and potential impact

BMI = body mass index; RCT= randomized controlled trial; ICD = International Classification of Disease; NRT = nicotine replacement therapy; TAU = treatment as usual; ITT = intention-to-treat; EMR = electronic medical record

Table 6: Strengths and Limitations of Guidelines using AGREE II[14]

Strengths	Limitations
National Institutes for Health and Care Excellence[35]	
-Review protocol for question related to smoking cessation interventions stated clearly -Assessed strength of evidence using GRADE -Interpretation of evidence by the Guideline Development Group, which involves a wide range of stakeholders including patients -Detailed description of search and development methods -Benefits and harm trade off considered by Guidelines Development Group in making the recommendations	-Updated 1 existing Cochrane on the topic review but did not consider other sources or systematic reviews -No evidence of external validation

Appendix 4: Main Study Findings and Author's Conclusions

Table 7: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
National Institute for Health and Care Excellence[35]	
From page 183: "7.3.8.1 Offer people with psychosis or schizophrenia who smoke help to stop smoking, even if previous attempts have been unsuccessful. Be aware of the potential significant impact of reducing cigarette smoking on the metabolism of other drugs, particularly clozapine and olanzapine. [new 2014] 7.3.8.2 Consider one of the following to help people stop smoking: • nicotine replacement therapy (usually a combination of transdermal patches with a short-acting product such as an inhalator, gum, lozenges or spray) for people with psychosis or schizophrenia or • bupropion for people with a diagnosis of schizophrenia or • varenicline for people with psychosis or schizophrenia. Warn people taking bupropion or varenicline that there is an increased risk of adverse neuropsychiatric symptoms and monitor them regularly, particularly in the first 2-3 weeks. [new 2014] 7.3.8.3 For people in inpatient settings who do not want to stop smoking, offer nicotine replacement therapy to help them to reduce or temporarily stop smoking. [new 2014]"	N/A
Bennett, 2013[16]	
-Three studies of NRT combined with psychosocial treatment suggest "can help smokers with schizophrenia reduce or quit smoking or maintain abstinence following quitting."- cessation rates ranged from 23.1% to 66% (pg 181) -Eight studies of buproprion alone or with NRT or a psychosocial intervention suggest "bupropion is associated with greater reduction and cessation than placebo while treatment is active but does not generally foster maintenance of gains once medication is removed" (pg 184), though it also does not make depression or schizophrenia symptoms worse - cessation rates ranged from no impact to 66% -Only two studies with varenicline are "promising" (pg 184)	"Overall, both pharmacologic and psychosocial smoking cessation treatments have been found to be useful in helping individuals" (pg 186)

Main Study Findings	Author's Conclusion
Ferron, 2009[17]	
NRT vs treatment as usual at 1 or 3 months follow up -Effect sizes ranged from 0.12 to 1.0 for follow up proportions (presumably abstinent) following arcsine transformations *Bupropion vs placebo at 3 months follow up* -Effect sizes ranged from 0 to 0.77 for follow up proportions (presumably abstinent) following arcsine transformations -Treatments not found to be toxic	"Preliminary data show modest efficacy of nicotine replacement therapy, psychosocial interventions and bupropion"(pg 64)
Kishi, 2015[19]	
Varenicline vs Placebo (5 papers; I2 = 94%) Smoking cessation: RR = 0.79 (95% CI 0.58, 1.08) Abnormal dreams: RR = 0.47 (95 % CI 0.22, 0.99, p = 0.05, I2 = 0 %) Nausea: RR = 1.79 (95 % CI 1.20,2.67, p = 0.004, I2 = 10 %) -No significant difference in the discontinuation rates, suicidal ideation, depression, other side effects	"Varenicline adjuvant therapy was not more efficacious than placebo for smoking cessation in individuals with SZ."(pg 265)
Peckham, 2017[21]	
Addition of buproprion to some intervention (8 trials; I2 = 0%) -Quit rate short term (median 4 weeks): RR = 6.42 (95% CI 0.82, 50.1) -Quit rate medium term (median 3.5 months): RR = 2.93 (95% CI 1.61, 5.34) -Quit rate long term (median 11.75 months): RR = 3.04 (95% CI 1.10, 8.42) *Varenicline versus placebo (5 trials, I2 = 0%)* -Quit rate medium term (median 6 months): RR = 4.13 (95% CI 1.36, 12.53) -No significant differences in changes in psychiatric symptoms across 22 studies, except one study found significant worsening of cognitive score in bupropion intervention group compared to placebo	"In line with the results of our previous review, this updated review indicates that people with [severe mental illness(SMI)] can quit smoking and the same interventions that work for people in the general population work for people with SMI e.g. the use of varenicline, bupropion or NRT to support a quit attempt" (pg 13)
Roberts, 2016[8]	
Network meta-analysis for smoking cessation -Bupropion vs placebo: OR = 4.51 (95% CI 1.45, 14.04) -Varenicline vs placebo: OR = 5.17 (95% CI 1.78, 15.06) -Bupropion vs varenicline: OR = 1.15 (95% CI 0.24, 5.45) *Direct pairwise meta-analysis for smoking cessation*	"Bupropion and varenicline are effective and tolerable for smoking cessation in adults with SMI. Both varenicline and bupropion had superior treatment efficacy to placebo and were not different from each other." (pg 7)

Main Study Findings	Author's Conclusion
-Bupropion plus NRT compared to placebo plus NRT: OR = 4.13 (95% CI 0.92, 18.47) *Tolerability* -No significant differences in drop-out rate in any of the comparisons	
Tsoi, 2010[6]	
Bupropion vs placebo End-of-treatment abstinence (6 trials, I2 = 0%): RR = 2.57 (95% CI 1.35, 4.88) 6-month abstinence (5 trials): RR = 2.78 (95% CI 1.02, 7.58) End-of-treatment expired CO (3 trials, I2 = 0%): Mean difference = -6.84 ppm (95% CI -11.11, -2.56) 6-month expired CO (3 trials, I2 = 83%): Mean difference = -5.73 ppm (95% CI -18.09, 6.63) -No significant worsening of positive, negative and depressive symptoms *Safety* -Significantly higher dry month, concentration, jitteriness, light-headedness, muscle stiffness and frequent nocturnal awakening reported in one study -Discontinuation from bupropion + NRT (n=2) due to insomnia and dizziness in one study	"Smokers with schizophrenia who used bupropion to aid smoking cessation had a two and a half times higher rate of abstinence at the end of the drug therapy compared with those who did not use bupropion….Although some side-effects of treatment that might be important to individuals were noted, there were no significant serious adverse clinical events such as seizure." (pg 349)
Tsoi, 2013[20]	
Bupropion vs placebo Smoking abstinence at 6-month follow up (5 trials, I2 = 0.00) RR = 2.78 (95% CI 1.02,7.58) Smoking abstinence at end of treatment (7 trials, I2 = 0.00) RR = 3.03 [1.69, 5.42] Change in Expired CO by end of treatment (4 trials, I2 = 0%): Mean difference = -6.80 ppm (95% CI -10.79, -2.81) Change in Expired CO at six months (3 trials, I2 = 83%): Mean difference =-5.55 ppm (95% CI -17.89, 6.78) Change in cigarettes per day at end of treatment in abstinence studies (3 trials, I2 = 40%): Mean difference = -10.77 (95% CI -16.52, -5.01) Change in cigarettes per day at end of treatment among reduction studies (2 trials): Mean difference = -2.61 (95% CI -7.99, 2.77)	"Our review supports the effectiveness of bupropion for smoking cessation in patients with schizophrenia…[we found] no evidence of any significant deterioration of mental state secondary to use of bupropion in people with schizophrenia…The evidence for bupropion as an aid to smoking reduction in people with schizophrenia is inconclusive." "We also found some evidence in support of varenicline for smoking cessation among individuals with schizophrenia...although there is no evidence that varenicline worsens symptoms in schizophrenia, there is some concern about serious adverse events such as suicidal ideation or behaviour among schizophrenia patients on varenicline" "For other drug treatments (including NRT) and psychosocial interventions, we did not find sufficient convincing evidence in to support their use in clinical practice." (pg 26-7)

Main Study Findings	Author's Conclusion
Change in cigarettes per day at six months (2 trials, I2 = 0%): Mean difference = 0.40 (95% CI -5.72, 6.53) -No significant differences between positive, negative or depressive symptoms *Varenicline vs placebo (2 trials)* -Abstinence at end of treatment (2 trials, I2 = 0%): RR = 4.74 (95% CI 1.34, 16.71) -Abstinence at 6-month follow up (1 trial): RR = 5.06 (95% CI 0.67, 38.24) -No significant differences between positive, negative or depressive symptoms -Change in cigarettes per day (1 trial): Mean difference = 3 (95% CI 0.4, 6.1) *TNP* -"Unclear whether transdermal nicotine patch (TNP) helped smoking cessation in this group of patients, as it was tested in only a few trials with small sample sizes" (pg 23)	
Wu, 2016[18]	
Varenicline versus placebo Abstinence rates at 12 weeks (four studies I2 = 0%, p = 0.91) RR = 4.33 (95% CI 1.96, 9.56) Reduction in number of cigarettes smoked at treatment end (five studies I2=89.2%): Mean difference = 6.39 (95% CI = 2.22, 10.46) Psychiatric symptoms (low number of events) Suicidal ideation (4 studies - I2 = 0%): RR = 1.06 (95% CI 0.40, 2.82) Depressed mood (3 studies - I2 = 28.6%): RR = 1.45 (95% CI 0.45,4.64) Anxiety (4 studies - I2 = 33.7%): RR = 0.77 (95% CI 0.28,2.17) Other side effects No significant differences between the groups across 35 types of adverse events Most common were nausea (n=46/158 varenicline vs n=25/114 placebo), abnormal dreams(n = 27/158 vs n = 24/114), abdominal pain (n = 25/158 vs n = 18/114), insomnia (n = 31/158 vs n = 21/114), fatigue/lethargy (n = 26/158 vs n = 17/114)	"The results of our meta-analysis suggest that varenicline reduced smoking significantly in people with SMI compared with placebo. Given that estimates of the rate of quitting vary markedly among studies, in terms of length of time quit, length of follow-up and means of measurement, the use of changes in daily cigarette consumption as a measurement of smoking behaviour change facilitates direct comparison across studies" (pg 111)

Main Study Findings	Author's Conclusion
Evins, 2017[10]	
SBD vs general population continuous abstinence rate at week 24 Overall: OR = 0.27, 95% CI: 0.13, 0.56, p<0.001 With varenicline: OR = 1.68, 95% CI: 0.53, 5.32, p = 0.38 With placebo: OR = 0.26, 95% CI: 0.13, 0.52, p < 0.001 *SBD versus general population point-prevalence abstinence hazard ratios [presented by author as OR]* With varenicline: OR = 0.99; p = 0.897 With placebo: OR = 0.87; p = 0.011 *Time to first relapse quartile 1 at 12 weeks[X^2 test p<0.0001]* SBD on placebo: Q1 = 12 days No SBD on placebo: Q1 = 17 days SBD on varenicline: Q1 > 95 days No SBD on varenicline: Q1 = 88	"Among those assigned to placebo, those with SBD were more likely to relapse and lapsed sooner than smokers without psychiatric illness...Among those on maintenance varenicline, the 6-month abstinence rates and time to first lapse was no different in those with SBD than for those without psychiatric illness."(pg 127)
Chen, 2013[23]	
Mean differences from baseline high vs low NRT (SD) -Daily number of cigarettes: -3.2 (7.1) vs -0.15 (7.5) -CO level: -0.1 (6.4) vs -0.6 (6.5) -FTND: -1.2 (2.3) vs -0.6 (2.4) -Positive and negative syndrome scale: -2.5 (11.0) vs -2.5 (11.0) -Simpson-Angus rating scale score: -0.02 (0.2) vs -0.02 (0.3) -7-day point prevalence abstinence: 1.1% (1/92) vs 4.3% (4/92) *Safety* -5 discontinued due to side effects (unspecified)	"In summary, among a cohort of chronic institutionalized schizophrenic patients who took part in smoking cessation programs, smoking cessation and reduction outcomes were not correlated with NRT dose, and the cessation rate was much lower than those in similar studies."(pg 80)
Dennis, 2016[24]	
Active versus placebo nicotine patch -Pre-quit phase (2 weeks) nicotine craving: t(59) = −1.17, p = 0.25 -Pre-quit phase (2 weeks) smoking: t(1340) = −0.74, p = 0.46 -Pre-quit phase (2 weeks) PTSD symptoms: F(5,230) = 0.47, p=0.80 -Post-quit phase time to relapse: HR=0.97, p=0.91 -Abstinence 6-weeks: OR = 1.54 (95% CI 0.23,10.15) -Abstinence 6-months: n=26 (100%) reported smoking	"We found that supplemental nicotine patch-preloading did not lead to reductions in craving and smoking during the preloading phase, nor was it associated with reductions in smoking-associated relief from PTSD symptoms and negative affect."(pg 28)
Stockings, 2014[22]	
NRT+ vs treatment as usual Fischer's exact tests for differences in continuous abstinence at 6 months:	"For smokers with a mental disorder, cessation support provided post-hospitalization was effective in reducing cigarette consumption and

Main Study Findings	Author's Conclusion
p = 0.26 Odds ratio for control (reference) vs intervention group at 6 months Point prevalence abstinence: OR = 1.32 (95% CI 0.47,4.36) Quit attempts: OR = 2.89 (95% CI 1.43, 5.98) 50% reduction in cigarettes per day: OR = 5.90 (95% CI 2.89, 15.25) Mean difference between control and intervention group at 6 months Cigarettes per day: −7.1 (95% CI −10.7 ,−3.5) p < .0001 Nicotine dependence (FTND): −1.6 (95% CI −2.3, −0.8) p < .0001 Psychological distress (K10): −0.7 (95% CI −3.7, 2.3) p=.642	nicotine dependence, and encouraging quit attempts at 6 months."
Jeon, 2016[26]	
Varenicline vs placebo (baseline to week 8) mNWS scores: p=0.391 QSU-brief: p=0.083 mCEQ: p=0.355 (time x group interaction p=0.002) Expired CO: p=0.019 (time x group interaction p= 0.046) Amount of cigarette: p=0.063 (time x group interaction p=0.007) PANSS total: p = 0.893 SANS: p = 0.170 HAM-D: p = 0.805 *Safety* -Three adverse events (3/60) including nausea (1/30 in each group), headache (1/30 in varenicline group) resulting in discontinuation, and two aggravated psychotic symptoms resulting in withdrawal between weeks 2 and 4	"Our results suggest that varenicline is effective for smoking reduction and is generally well-tolerated and safe in combination with antipsychotics for patients with schizophrenia" (pg 210)
Garcia-Portilla, 2016[28]	
Varenicline vs TNP mean differences (Week 12, 24, 36) -[Week 12] 7-day point prevalence abstinence: Mean difference = 1.4% (chisquare = 0.015, p=1.000) -[Week 12] >= 50% reduction in the number of cigarettes per day: Mean difference = 2.9%, chi-square= 0.100, p=0.776) -[Week 24] 7-day point prevalence abstinence: Mean difference = 7.9% (chisquare = 0.475, p = 0.639) -[Week 24] >= 50% reduction in the number of cigarettes per day: Mean difference = 1.8%, chi-square = 0.030, p = 1.000) -[Week 36] 7-day point prevalence abstinence: Mean difference = 16.4% (chi-square = 2.153, p=0.159) -[Week 36] >= 50% reduction in the number of cigarettes per day: Mean	"After 12 weeks of treatment with TNP or varenicline, combined with group therapy, a smoking cessation rate of 50% was achieved...As expected, this rate decreased with time, but 6 months after the end of the acute-treatment phase, 37% of patients in the trial remained abstinent. There were no differences in the dropout rates between the two drugs at any point in the study. Both pharmacological treatments were safe and generally well tolerated." (pg 276)

Main Study Findings	Author's Conclusion
difference = 0.7%, chi-square = 0.005, p = 1.000) *Other effects* -No observed group differences over time in breath CO level, FTND scores, GN-SBQ scores or proportion of mild, moderate, heavy smokers *Safety* -Significant weight gain in both groups -Varenicline group had significantly lower cholesterol levels -21/36 (58.3%) in TNP and 27/39 (69.2%) in varenicline group experienced at least 1 AE, most commonly abnormal/vivid dreams (n=9 and n=4, respectively), constipation (n=5 and n=9, respectively), and nausea/vomiting in varenicline group only (n=12; p < 0.0005)) -4/39 (10.2%) switched to TNP due to adverse event and 3/39 (7.8%) reduced their varenicline dose	
Stapleton, 2008[27]	
Total population including those without mental illness at 8 weeks -2-week abstinence prevalence NRT vs varenicline: OR = 1.70 (95% CI 1.09, 2.67) Mean Difference=10.8% (95% CI 1.8%, 19.9%) *Population with mental illness only at 8 weeks* -2-week abstinence prevalence NRT vs varenicline: OR = 2.88 (95% CI 1.08, 7.63) Mean difference=16.5% (95% CI -0.01%, 34.2%) *Safety* -Significantly higher nausea, disturbed sleep, vivid dreams, drowsiness, constipation, headache, dyspepsia, dry mouth, bad taste, low mood, diarrhoea and disorientation in varenicline group -7 patients switched from varenicline to NRT due to adverse symptoms (unspecified) -Adverse symptoms not found to be higher or more severe in those with mental illness	"The results suggest that, with routine psychological and behavioural group support, varenicline is more effective than NRT in aiding short-term smoking cessation...The results also indicate that varenicline is similarly effective in those with mental illness, supporting the regulatory decision to allow varenicline treatment in these patients" (pg 152)
Brody, 2017[25]	
7-day point prevalence abstinence at 6 months -TAU vs treatment (no home visits): $\chi 2(1) = 0.7$, p = .4 -TAU vs treatment (with home visits): $\chi 2(1) = 4.8$, p = .03 *Change in cigarettes per day at week 0 versus week 26* -TAU vs treatment (no home visits): -7.5 vs -14 (p < 0.05) -TAU vs treatment (with home visits): -7.5 vs -16.1 (p < 0.05)	"In conclusion, rapidly initiated combination and extended treatment improves smoking reduction/cessation outcomes compared to TAU in smokers with schizophrenia. In addition, [home visits] appear to be a promising adjunct to encourage smoking reduction and abstinence, and may be worthy of future research." (pg 74)

Main Study Findings	Author's Conclusion
Change in *exhaled carbon monoxide level at week 0 versus week 26* -TAU vs treatment (no home visits): -0.8 vs -7.3 ($p < 0.05$) -TAU vs treatment (with home visits):-0.8 vs -7.0 ($p < 0.05$) *Change in FTND score at week 0 versus week 26* -TAU vs treatment (no home visits): -2.2 vs -3.0 -TAU vs treatment (with home vists): -2.2 vs -4.2 ($p < 0.05$) *Safety* -No significant changes in safety measures from baseline scores in BPRS, SANS, CGI, BDI, C-SSRS, AIMS -27%, 30% and 46% reported adverse events in treatment with home visits, treatment without home visits and TAU groups respectively, most commonly insomnia (n = 4), with vivid dreams (n = 2), nausea (n = 2), rash (n = 2), agitation (n = 1)	
Castle, 2012[33]	
Baseline vs 6-months mean differences Cigarettes per day: B = 13.61 (95% CI 6.58, 20.75), p= 0.001 Expired CO: B = 9.23 (95% CI -5.04, 23.51), p = 0.02 Dependence (FTND): B = 2.1 (95% CI 0.48, 3.62), p = 0.01 Withdrawal (other-rated): B = -0.32 (95% CI -0.63, -0.001), p = 0.05 Withdrawal (self-rated): B = 1.3 (95% CI 0.06, 0.61), p = 0.02 *Safety* -Most common side effects were sleep disturbance and nausea (exact number unclear) -3/14 patients discontinued due to psyciatric issues (n=1) or nausea (n=2) -No significant changes in MNWS, BPRS, BDI from baseline to follow up (BDI (pre: 9.2 [SD 7.0], post: 8.1 [SD 8.1]); YMRS (pre: 3.8 [SD 5.5], post 4.9 [SD 6.0]); or BPRS (pre: 35.6 [SD 5.0], post: 39.8 [SD 8.9]).	"This open study demonstrated that varenicline, in association with a comprehensive healthy lifestyle intervention, was associated with a substantial decrease in cigarette smoking among a heterogeneous group of patients with psychotic disorders. Abstinence was achieved in 42% of the participants at the 6-month mark. Side effects were mostly nonpsychiatric (ie, sleep disturbance, nausea) and transient; 1 patient with [bipolar disorder] dropped out because of a severe worsening of depression with suicidality." (pg 288)
Cather, 2017[34]	
-74 participants (41.3%) attained 2+ weeks of continuous abstinence at the end of 12-week varenicline treatment period (mean = 42.7 +/- 18.6 days) *Other symptoms* -CDSS scores decreased over time with varenicline treatment in the abstinent-achieving group ($F(13, 816) = 6.22$, $p < .001$) and non-abstinent completers ($F(13, 841) = 2.48$, $p = .003$_ but not , study dropouts ($F(12, 1349) = 1.48$, $p = .125$) -WSWS scores decreased over time significantly in those who attained	"We conclude that smokers with schizophrenia and schizoaffective disorder who have significant depressive symptoms may be successful in smoking cessation attempts with varenicline while maintaining stable psychiatric symptoms." (pg 8)

Main Study Findings	Author's Conclusion
abstinence F(13,820) = 1.76, p = .046, but not among non-abstinent completers (F(13, 850) = 1.29, p = .210), or those who dropped out (F(12, 1340) = 1.09, p = .368.)	
Raich, 2016[31]	
Abstinence at week 12 -All remaining subjects (n=37 (41.1%)) were abstinent at Week 12 *Safety* -53/90 discontinued; 4/53 discontinued due to adverse events (unspecified) -Most common adverse events were dry mouth (n=26; 28.9%), flatulence (n=25; 27.8%), abnormal dreams (n=25; 27.8%) and nausea (n=20; 22.2%) -2 patients with 'moderate suicidal ideation' during weeks 2 and 6, one of whom discontinued	"The present study shows smoking cessation with varenicline presents an acceptable safety level in patients with psychiatric disorders (psychotic disorder, alcohol dependence, and opioid dependence). Gastrointestinal adverse events are the most prevalent, although treatment dropout rates with varenicline are very low" (pg 652)
Pachas, 2012[32]	
Mean change per week from baseline to 12 weeks -CO: B =−0.03 (SE = 0.01), p < 0.01 -7-day abstinence: B= 0.34 (SE = 0.03), p < 0.01 -WSWS: B=−0.65 (SE =0.15), p < 0.01 -Urge to Smoke: B= −0.29 (SE =0.04), p < 0.01 -Calgary Depression Scale: B = −0.14 (SE =0.01), p < 0.01 -BPRS -Psychosis: B= -1.34 (t=2.815, p< 0.01) -SANS Total: B= -1.0 (t=−0.914) *Safety* -Most frequent adverse event was transient nausea -n=3/110 psychiatric hospitalizations (with 1 for paranoia and suicidal ideation) -n=12/110 discontinued study (nausea (5), anxiety (2), weight gain (1), depressed mood (1), paranoia (1), suicidal ideation (1), and substance use (1)) -Significant weight gain was observed on average (B=202.59 (SD=44.35) at baseline to B=207.6 (SD=45.4) pounds at 12 weeks)	"Over 12 weeks, participants demonstrated increased abstinence rates, and decreased withdrawal symptoms, depressive symptoms and psychosis. The most common AE was transient nausea"(pg 6)
Loreto, 2017[30]	
Among patients with mental disorder OR for abstinence compared to nicotine patch only [95% CI]:	"The use of CBT plus combined pharmacotherapy (NRT patch plus gum or bupropion) could be a powerful smoking cessation intervention in

Main Study Findings	Author's Conclusion
Nicotine patch plus bupropion 2.00 [1.14, 3.50] Nicotine patch plus gum 2.10 [1.04, 4.23] Nicotine patch plus nortriptyline 2.07 [0.53, 8.08] HR for treatment retention compared to nicotine patch only [95% CI]: Nicotine patch plus bupropion 0.87 [0.60, 1.26] Nicotine patch plus gum 0.70 [0.42, 1.14] Nicotine patch plus nortriptyline 0.68 [0.27, 1.71] *Among patients without mental disorder* OR for abstinence compared to nicotine patch only [95% CI]: Nicotine patch plus bupropion 1.51 [0.97, 2.35] Nicotine patch plus gum 1.17 [0.62, 2.21] Nicotine patch plus nortriptyline 1.96 [0.65, 5.96] HR for treatment retention compared to nicotine patch only [95% CI]: Nicotine patch plus bupropion 0.77 [0.57, 1.05] Nicotine patch plus gum 0.96 [0.62, 1.47] Nicotine patch plus nortriptyline 0.79 [0.36, 1.72]	patients with MD, more so than in patients without MD." (pg 7)
Wu, 2017[29]	
Hazard ratio for suicide attempts/behaviours (relative to Varenicline group) NRT: HR = 0.81 (95% CI 0.51, 1.28) Bupropion: HR = 0.37 (95% CI 0.05, 2.70)	"Our study was the first to examine suicide behaviors or attempts among this minority population and we did not find any differences between the medications." (pg 67)

95% CI = 95% confidence interval; OR = odds ratio; RR = risk ratio; HR = hazard ratio, AE = adverse event, SMI = severe mental illness; SBD = schizophrenia or biopolar disorder; TAU = treatment as usual; NRT = nicotine replacement therapy; TNP = transdermal nicotine patch; CO = carbon monoxide; ppm = parts per million; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders; CBT = cognitive behavioural therapy; FTND = Fagerstrom Test for Nicotine Dependence; mNWS = Minnesota Nicotine Withdrawal Scale; WSWS = Wisconsin Smoking Withdrawal Scale; mCEQ = Modified Cigarette Evaluation Questionnaire; BPRS = Brief Psychiatric Rating Scale; SARS = Simpson-Angus Rating Scale; PANSS = Positive and Negative Syndrome Scale; HAM-D = Hamilton Rating Scale for Depression; CDSS = Calgary Depression Scale for Schizophrenia; BDI = Beck Depression Inventory; C-SSRS = Columbia- Suicide Severity Rating Scale; AIMS = Abnormal Involuntary Movement Scale; K10 = Kessler Psychological Distress Scale; CGI = Clinical Global Impression; QSU = Questionnaire of Smoking Urges

Appendix 5: Additional References of Potential Interest

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