SMOKING CESSATION IN MENTAL HEALTH SERVICES

Review 4: Effectiveness of Smoking cessation interventions in Mental health

PRODUCED BY: UK Centre for Tobacco Control Studies (UKCTCS, http://www.ukctcs.org/)

REVIEW TEAM: Dr Jo Leonardi-Bee, UKCTCS, University of Nottingham

Leah Jayes, UKCTCS, University of Nottingham

Alison O'Mara-Eves, EPPI-Centre, Institute of Education, University of London

Claire Stansfield, EPPI-Centre, Institute of Education, University of London

Kate Gibson, EPPI-Centre, Institute of Education, University of London

Dr Elena Ratschen, UKCTCS, University of Nottingham

Professor Ann McNeill, UKCTCS, University of Nottingham

DATE: 30 November 2012

VERSION: Draft 5.0

November 2021: NICE guidelines PH45 (June 2013) and PH48 (November 2013) have been updated and replaced by NG209.
The recommendations labelled [2013] or [2013, amended 2021] in the updated guideline were based on these evidence reviews.
See www.nice.org.uk/guidance/NG209 for all the current recommendations and evidence reviews.

CONTENTS PAGE

ACKNOWLEDGEMENTS

The review team would like to thank Irene Kwan from the EPPI-Centre, Institute of Education, University of London, and Professor Sarah Lewis from the UK Centre for Tobacco Control Studies, University of Nottingham, for their contributions to the work within the report. We would also like to thank the members of the PDG and the team at NICE for their comments.

TABLES PAGE

FIGURES PAGE

EXECUTIVE SUMMARY

BACKGROUND

The strong relationship between smoking and severe mental illness, as well as the complexity of neurobiological, environmental and genetic factors contributing to it, are well recognised. Smoking prevalence among people diagnosed with a severe mental illness, such as schizophrenia, can reach 70% or more, by far exceeding prevalence in the general population (21%), and levels of tobacco dependency have also been found to be higher. Much of the excess mortality and morbidity in people with severe mental illness has been found to be associated with smoking related conditions, and rates of cardiovascular and respiratory diseases as well as cancers are increased compared to the general population. Although smoking has been identified as one of the major contributors to health inequalities in this population, smoking is still the norm in many mental health settings, and no best practice models for the provision of effective support in mental health settings have been identified.

AIM OF THE REVIEW

To assess the effectiveness of smoking cessation and temporary abstinence interventions in mental health services, including strategies for referring people to stop smoking or hospital based stop smoking services, for the populations of interest.

QUESTIONS OF THE REVIEW

The review will address the following key research questions:

i) How effective are smoking cessation interventions in helping people from the populations of interest?

ii) How effective are interventions for temporary abstinence in helping people from the populations of interest?

iii) How effective are current strategies/approaches used by secondary care mental health services for identifying and referring people from the population of interest to stop smoking or hospital based stop smoking services?

iv) How effective are current strategies/approaches used by secondary care mental health services for identifying and providing people from the population of interest with smoking cessation information, advice and support?

v) Which strategies/approaches are effective in encouraging mental health care professionals to record smoking status and refer populations of interest to stop smoking services?

Subsidiary questions include:

- *How does the effectiveness of smoking cessation and temporary abstinence interventions vary by mental health diagnosis, gender, sexual orientation, age, ethnicity, religion, socioeconomic status, disability, and by populations of interest (including patients, household members, visitors and staff)?*
- *Are there differences in the effectiveness of smoking cessation and temporary abstinence interventions by deliverer, timing (or point in the care pathway), frequency, duration, and severity of dependence, and setting in which the intervention is assessed, for example in-patients versus out-patient?*
- *What are the adverse events and other consequences associated with using smoking cessation and temporary abstinence interventions in the populations of interest?*

METHODS

A comprehensive systematic review was conducted to address the questions of the review. A comprehensive search strategy of electronic databases, websites, and reference screening was performed, with searches being conducted in February 2012. We considered comparative epidemiological studies which include the following populations of interest of any age who smoke:

  - All users of secondary care mental health services, including those who are in the process of being referred to or have recently been discharged from child, adolescent, adult or older people mental health services:
    - In-patient, residential and long-term care for severe mental illness in hospitals, psychiatric and specialist units and secure hospitals
    - Patients who are within the care of specialist community-based multidisciplinary mental health teams
- People living in the same household as a mental health service user, such as partners, parents, other family members and carers
- Visitors to secondary care mental health setting who are not receiving treatment or care, such as relatives or friends of patients or service users
- Staff (including support staff, volunteers, agency/locum staff and staff employed by contractors) working in secondary care mental health settings, in particular those who have direct contact with patients and service users

We included any pharmacological, psychological, behavioural, or self-help intervention that aims to assist with smoking cessation or temporary abstinence. We included any strategies, protocols or systems used by relevant health professionals to help identify smokers, record advice given and refer them to services, alone and share information between different groups of health professionals and across the care pathway. Primary outcomes of interest included the proportion of participants who made successful quit attempts; changes in mean biochemically validated levels of smoking from baseline; and self-reported cigarette consumption. Other outcomes included an assessment of current strategies using the number of referrals to and contacts with stop smoking services; a comparison of the number of smoking cessation referrals between mental health care and other settings; assessments of improvement in health (for example, recovery rates); changes in recording or referral procedures or care pathway development, following targeted interventions to

support the implementation of tobacco treatment services in mental health settings. Further outcomes of interest included measures of self-efficacy, nicotine dependence and withdrawal, motivation, confidence, where these were reported in addition to assessing smoking cessation ascertained as described above. We additionally assessed the proportion of populations of interest with adverse events.

Two reviewers independently screened 10% of titles and abstracts, and full texts to ensure high agreements between reviewers. The remaining titles and abstracts, and full texts were then screened by one of the reviewers. 10% of the included studies were independently data extracted and quality assessed by two reviewers to ensure high agreement; then the remaining papers were extracted by one of the reviewers. Meta-analyses were conducted using random effect models, with heterogeneity quantified using I^2. Data are presented as odds ratios (OR) with 95% confidence intervals (CI). P values<0.05 were deemed statistically significant.

Evidence statements based on an aggregated summary of the available evidence were produced, which reflected the strength (quality, quantity and consistency) of the evidence and statements regarding its applicability were made. The quality of the evidence was categorised as strong (where statements were based on evidence from several high quality studies), moderate (where statements were based on evidence from either one high study, or a mixture of high and lower quality studies), weak (where statements were based on evidence from lower quality studies), or very weak (where statements were based on evidence from individual lower quality studies). Statements were also made where there is a lack of evidence. Statements regarding the applicability of the evidence to the UK setting were also reported and categorised as directly applicable, potentially applicable, or not applicable.

RESULTS

51 studies were included, with the majority focusing on populations with schizophrenia. The majority of studies were conducted in outpatient mental health populations, and most studies recruiting participants directly from the users of particular outpatient or in-patient mental health care clinics. 41 studies were based on USA populations. The sample size of the studies ranged from 5 to 943. The interventions for smoking cessation under assessment in the studies were behavioural therapy (high intensity, 11 studies; low intensity, 2 studies), nicotine replacement therapy (6 studies), bupropion (10 studies), clozapine (3 studies), or NRT with behavioural therapy (3 studies), combination of NRT with bupropion (3 studies), and four studies were identified which assessed the effectiveness of varenicline. Single studies assessed the effectiveness of contingency payments; fluoxetine, galantamine, naltrexone, contingency payments with either bupropion or NRT. The interventions in the studies which were specifically assessed for smoking reduction were bupropion (1 study), bupropion with behavioural therapy (1 study), and contingency payment with NRT (1 study). The majority of studies used a parallel group RCT design.

EVIDENCE STATEMENTS

i) How effective are smoking cessation interventions in helping people from the populations of interest? Subsidiary question includes: What are the adverse events and other consequences associated with using smoking cessation and temporary abstinence interventions in the populations of interest?

EVIDENCE STATEMENTS – HIGH INTENSITY BEHAVIOURAL THERAPY (WITHOUT PHARMACOTHERAPIES)

EFFECTIVENESS

ES1.1 There is moderate evidence from two trials (**McFall 2005 [RCT, USA, +]; McFall 2010 [RCT, USA, +]**) to suggest integrated tailored behavioural therapy was more effective for increasing smoking cessation in outpatients for PTSD in the short (pooled OR 3.04, 95% CI 1.65-5.60) and long (OR 1.83, 95% CI 1.26-2.66) term than usual standard of care (referral to a specialised smoking cessation clinic).

ES1.2 There is mixed weak evidence from four studies regarding the effectiveness of high intensity behavioural therapy in people with psychiatric disorders. One study (**Currie 2008 [Quasi-RCT, Canada, +]**) suggested high intensity behavioural therapy given for 8 weeks was marginally more effective than given for 4 weeks in outpatients; however no formal comparisons could be made to assess statistical significance. Evidence was mixed from two further studies where one study demonstrated no significant difference in abstinence between motivational interviewing or brief advice in 191 in-patients **(Brown 2003 [RCT, USA, +]**; long term outcome, OR 1.16, 95% CI 0.59-2.31), whereas the other demonstrated significantly fewer people smoked at short term follow-up in the high intensity behavioural therapy group compared to no intervention in 38 outpatients (**Kisely 2003 [NRCT, Australia, -])**. However, there was evidence from one study of 123 outpatients (**Morris 2011 [RCT, USA, +]**) which suggested high intensity behavioural therapy in addition to a quit-line service was more effective than quit-line service alone for reducing cigarette consumption (OR 3.16, 95% CI 1.04-9.65).

ES1.3 There is moderate evidence from three studies (**George 2000 [quasi-RCT, USA, +]; Wojtyna 2009 [NRCT, Poland, -]; Williams 2010 [RCT, USA, +]**) to suggest high intensity behavioural therapy is no more effective than lower intensity behavioural therapy for smoking cessation in the short (Pooled OR 1.20, 95% CI 0.39-3.72) or medium (OR 0.56, 95% CI 0.10-3.15) term in in-patients and outpatients with schizophrenia. Please note that two of these studies (**George 2000 [quasi-RCT, USA, +]; Williams 2010 [RCT, USA, +])** gave all participants NRT in addition to their behavioural therapy, and the intensity of the behavioural therapy in the control group of the **Williams 2010 [RCT, USA, +]** was relatively high.

The majority of evidence on high intensity behavioural therapy is directly applicable to the UK setting, as there is no reason to assume that the interventions could not be implemented in UK

outpatient and in-patient settings. Six of the studies were conducted in the USA, with individual studies being conducted in Australia, Canada, China, and Poland.

Unintended Consequences

ES19.1 There was moderate evidence from one trial (**McFall 2010 [RCT, USA, ++]**) to suggest smoking cessation arising from using high intensity behavioural therapy does not result in any adverse effects relating to psychiatric hospitalisation, cardiac or gastrointestinal related events in 943 outpatients with PTSD. This evidence is applicable to the UK setting.

ES24.1 There is moderate evidence from three trials in populations with mental health disorders (**Kisely 2003 [NRCT, Australia, -]; Currie 2008 [quasi-RCT, Canada, +]; Morris 2011 [RCT, USA, +]**) to suggest high intensity behavioural therapy programmes did not worsen mental health outcomes compared to standard behavioural therapy programmes on psychiatric symptoms.

ES24.2 There is moderate evidence from two trials focusing on populations with schizophrenia (**George 2000 [quasi-RCT, USA, +]; Williams 2010 [RCT, USA, +]**) to suggest high intensity behavioural therapy programmes did not worsen mental health outcomes compared to standard behavioural therapy programmes on psychiatric symptoms.

ES24.3 There is moderate evidence from two trials focusing on populations with PTSD (**McFall 2005 [RCT, USA, +]; McFall 2010 [RCT, USA, ++]**) to suggest high intensity behavioural therapy programmes did not worsen mental health outcomes compared to standard behavioural therapy programmes on psychiatric symptoms.

There is no reason to assume that unintended consequences related to the use of high intensity behavioural therapy programmes are not applicable to the UK setting.

Evidence statements – Low Intensity Behavioural Therapy (without Pharmacotherapy)

Effectiveness

ES2.1 There is very weak evidence from one RCT in 128 mental health outpatients (**Axtmayer 2011 [RCT, USA, -]**) to suggest brief intervention either from using a Quitline or a face-to-face counsellor resulted in a significant reduction in the number of cigarettes smoked per day from baseline (Mean reductions from 16.1 to 9.3 cigarettes/day, 17.9 to 11.1 cigarettes/day, respectively).

ES2.2 There is moderate evidence from one cluster RCT in 304 outpatients with schizophrenia or schizoaffective disorders (**Dixon 2009 [cluster RCT, USA, ++]**) to suggest low intensity behavioural support resulted in no significant difference in abstinence or smoking consumption.

The evidence from the two studies based on low intensity behavioural therapy is directly applicable to the UK setting as there is no reason to assume the interventions could not be implemented in UK outpatient and in-patient settings. Both studies were conducted in the USA.

EVIDENCE STATEMENT – CONTINGENCY PAYMENTS

EFFECTIVENESS

ES3.1 Weak evidence from one non-randomised within-subject reversal design trial (**Roll 1998 [NRCT, USA, -]**) suggested contingency payments rewards significantly reduced expired CO levels in 11 outpatients undergoing treatment for schizophrenia or schizoaffective disorders.

The evidence for contingency payments as an intervention for smoking cessation is potentially applicable to the UK as intervention may be feasible to the UK setting; however, this does not reflect current clinical practice in the UK. The study was conducted in the USA.

EVIDENCE STATEMENTS - BUPROPION

EFFECTIVENESS

ES4.1 There is weak evidence from one trial (**Hertzberg 2001 [RCT, USA, +]**) to suggest bupropion (300mg/day) is not effective for smoking cessation at short term follow-up in 15 male outpatients with PTSD.

ES4.2 There is very weak evidence from one trial (**Weinberger 2008 [RCT, USA, -]**) to suggest bupropion (300mg/day) is not effective for smoking cessation at short term follow-up in 5 outpatients with bipolar disorder.

ES4.3 There is strong evidence from pooled analyses comprising a total of five trials (**George 2002 [RCT, USA, ++]; Weiner 2011b [RCT, USA, ++]; Evins 2007 [RCT, USA, ++]; Evins 2001 [RCT, USA, +]; Evins 2005 [RCT, USA, ++]**) that bupropion (300mg/day) is effective for increasing smoking cessation in the short term in outpatients with schizophrenia (Pooled OR 3.80, 95% CI 1.58-9.15); but mixed strong evidence from pooled analyses comprising a total of three trials (**Evins 2007 [RCT, USA, ++]; George 2002 [RCT, USA, ++]; Evins 2005 [RCT, USA, ++]**) regarding the effectiveness of bupropion (300mg/day) for smoking cessation in the medium term in outpatients with schizophrenia (continuous abstinence, OR 3.00, 95% CI 1.29-7.00; point prevalence abstinence, pooled OR 2.80, 95% CI 0.51-15.53). Also, there is moderate evidence from one trial (**Evins 2007 [RCT, USA, ++]**) that bupropion is not effective for smoking cessation in the long term in outpatients with schizophrenia (OR 1.60, 95% CI 0.23-11.01).

ES4.4 There is moderate evidence from pooled analysis of two trials (**Evins 2007 [RCT, USA, ++]; Evins 2001 [RCT, USA, +]**) that bupropion (300mg/day) is effective for smoking reduction in the short term (Pooled OR 4.81, 95% CI 1.36-17.08) and medium (Pooled OR 5.11, 95% CI 1.28-20.39) term in outpatients with schizophrenia; however, there is very weak evidence from one trial (**Fatemi 2005 [RCT, USA, -]**) to suggest bupropion (dose not stated) had no significant effect on smoking reduction assessed as number of cigarettes per day smoked in outpatients with schizophrenia.

The evidence from the studies based on bupropion is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical

prescribing practice in the UK. The majority of studies were conducted in the USA, with individual studies being conducted in China, Iran, and Israel.

Adverse Events

ES20.1 There is strong evidence from 10 trials (**George 2002 [RCT, USA, ++]; Weiner 2011b [RCT, USA, ++] ; Bloch 2010 [RCT, Israel, –]** ; **Evins 2007 [RCT, USA, ++]; Evins 2005 [RCT, USA, ++]; Evins 2001 [RCT, USA, +] ; Li 2009 [RCT, China, –]**; **Tidey 2011 [RCT, USA, ++]; Fatemi 2005 [RCT, USA, -]; George 2008 [RCT, USA, ++]**) to suggest that bupropion was well tolerated in participants diagnosed with schizophrenia or schizoaffective disorders, with expected side effects of bupropion being seen (relating to dry mouth, nausea and headaches).

ES20.2 There is weak evidence from one trial (**Hertzberg 2001 [RCT, USA, +]**) to suggest bupropion was well tolerated in 15 male outpatients with PTSD.

ES20.3 There is very weak evidence from one trial (**Weinberger 2008 [RCT, USA, –]**) to suggest bupropion was well tolerated in 5 outpatients diagnosed with bipolar disorder.

Adverse events related to the use of bupropion are likely to be applicable to the UK setting, as there are no reasons to assume otherwise.

Unintended Outcomes

ES25.1 There is moderate evidence from eight trials (**Hertzberg 2001 [RCT, USA, +]; George 2002 [RCT, USA, ++]; Arkbapour 2010 [RCT, Iran, +]; Weiner 2011b [RCT, USA, ++]; Evins 2007 [RCT, USA, ++]; Evins 2005 [RCT, USA, ++]; Evins 2001 [RCT, USA, +]; Fatemi 2005 [RCT, USA, -]**) to suggest bupropion (predominately given at 300mg/day) did not worsen mental health outcomes in participants with schizophrenia or schizoaffective disorders.

ES25.2 There is moderate evidence from one trial (**George 2002 [RCT, USA, ++]**) to suggest that whilst bupropion (300mg/day) resulted in no significant difference in positive symptoms of schizophrenia, there was a significant reduction in negative symptoms of schizophrenia.

ES25.3 There is weak evidence from one trial (**Evins 2001 [RCT, USA, +]**) to suggest bupropion (150mg/day) significantly reduces weight in the short term in 18 outpatients diagnosed with schizophrenia.

ES25.4 There is very weak evidence from one trial (**Weinberger 2008 [RCT, USA, -]**) to suggest bupropion (300mg/day) has no detrimental effect on mood changes in 5 outpatients with bipolar disorder.

Unintended consequences related to the use of bupropion are likely to be applicable to the UK setting, as there are no reasons to assume otherwise.

Evidence Statement - Clozapine

Effectiveness

Clozapine is an atypical (new generation) antipsychotic medication. Switching from typical antipsychotic medications to atypical antipsychotic medications has been suggested to reduce smoking.

ES5.1 There is moderate evidence from three trials (**McEvoy 1995 [RCT, USA, -]; McEvoy 1999 [RCT, USA, +]; De Leon 2005 [RCT, USA, +]**) suggesting higher doses of clozapine (350-600mg/day) in in-patients with schizophrenia or schizoaffective disorders may reduce the self-reported number of cigarettes smoked per day; however, no effects were seen on objective markers of smoking consumption (expired CO or plasma nicotine levels).

The evidence from the three studies based on clozapine as a smoking cessation medication is potentially applicable to the UK setting as there is no reason to assume that the intervention would not have the same outcome in a UK setting. All three studies were conducted in the USA.

Unintended consequences

ES26.1 There is weak evidence from two trials (**McEvoy 1995 [RCT, USA, -]; McEvoy 1999 [RCT, USA, +]**) to support the assumption that moderate to high plasma levels (200-450ng/ml) of clozapine are significantly more likely to reduce psychiatric symptoms and severity of symptoms in schizophrenia than lower plasma levels (50-150ng/ml).

Unintended consequences as a result of using clozapine are likely to be applicable to the UK setting, as there is no reason to assume that this would not be the case.

Evidence statement – Fluoxetine

Fluoxetine is an antidepressant from the selective serotonin reuptake inhibitor (SSRI) class. It has been suggested that antidepressant, such as fluoxetine, may be effective for smoking cessation.

Effectiveness

ES6.1 There is weak evidence from one trial (**Cornelius 1997 [RCT, USA, +]**) of 25 in-patients with major depression suggested fluoxetine (40mg/day) had no significant effect on the number of cigarettes smoked per day in the short term.

The evidence from the individual study on fluoxetine as a smoking cessation medication is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. The study was conducted in participants with co-morbid alcohol dependence in the USA.

EVIDENCE STATEMENT - GALANTAMINE

Galantamine is an alkaloid that is used for the treatment of mild to moderate Alzheimer's disease and other memory impairments. It has been suggested that galantamine may be useful for smoking cessation.

EFFECTIVENESS

ES7.1 There is very weak evidence from one RCT of 42 inpatients and outpatients with schizophrenia (**Kelly 2008 [RCT, USA, -]**) of no effect of galantamine (maximum dose of 24mg/day) on self-reported and objective markers of cigarette use in the short term.

The evidence from the individual study on galantamine as a smoking cessation medication is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. The study was conducted in the USA.

EVIDENCE STATEMENT – NALTREXONE

Naltrexone is an opioid receptor antagonist which is used for the treatment of alcohol dependence and opioid dependence.

EFFECTIVENESS

ES8.1 There is moderate evidence from one RCT in 79 outpatients diagnosed with schizophrenia or schizoaffective disorders with co-morbid alcohol dependence that naltrexone (50g/day) had no significant effect on abstinence or self-reported numbers of cigarettes smoked per day (**Szombathyne-Meszaros 2010 [RCT, USA, +]**).

The evidence from the individual study on naltrexone as a smoking cessation medication is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. The study was conducted in participants with co-morbid alcohol dependence in the USA.

EVIDENCE STATEMENTS – NICOTINE REPLACEMENT THERAPY

EFFECTIVENESS

ES9.1 There is moderate evidence from one trial (**Hartman 1991 [RCT, USA, ++]**) to suggest NRT (8mg given once) is effective for smoking reduction in the very short term (7 hours follow-up) in 14 in-patients and outpatients with psychiatric disorders.

ES9.2 There is weak evidence from one trial (**Williams 2007 [RCT, USA, +]**) to suggest there is no significant benefit in smoking cessation from using high dose NRT (42mg patch) compared to standard dose NRT (21mg patch) in the short term in 51 outpatients with schizophrenia.

ES9.3 There is mixed very weak evidence from two trials (**Dalack 1999 [NRCT, USA, -]; Chou 2004 [RCT, China, -]**) regarding the effectiveness of standard dose NRT (22mg/24hr or 14mg/day) for smoking reduction or cessation in schizophrenia, where a significant decrease in mean expired CO levels was seen on the day following the patch application, but no reduction in the number of cigarettes smoked in one trial (**Dalack 1999 [NRCT, USA, -]**). In the other trial (**Chou 2004 [RCT, China, -]**), significant reductions in expired CO levels, self-reported number of cigarettes smoked per day and point prevalence abstinence (bio-verified by CO<10ppm) were seen in the NRT patch compared to placebo.

ES9.4 There is mixed weak evidence from two trials (**Thorsteinsson 2001 [RCT, USA, +]; Hill 2007 [NRCT, USA, -]**) regarding the effectiveness of standard dose NRT (21mg/24hr or 14mg/day) for smoking reduction or cessation in major depression, where smoking cessation was significantly more likely in the short term in one study (**Thorsteinsson 2001 [RCT, USA, +]**), but no significant difference was seen in the number of cigarettes smoked in the short term in the other study (**Hill 2007 [NRCT, USA, -]**).

The evidence from the studies on NRT is applicable to the UK setting as the study was predominately based on outpatient populations with mental health disorders, and the intervention reflects current clinical prescribing practice in the UK for smoking cessation, and could be feasible within populations with mental health disorders. The studies were conducted predominately in the USA, with a further study being conducted in China.

ADVERSE EVENTS

ES21.1 There is moderate evidence from four trials (**George 2000 [quasi-RCT, USA, +]; Dalack 1999 [NRCT, USA, +]; Williams 2007 [RCT, USA, +]; Tidey 2002 [NRCT, USA, –]**) to suggest standard dose NRT patches (21 or 22mg/day) are well tolerated in participants with schizophrenia or schizoaffective disorders, with expected side effects being reported (irritability at patch site).

ES21.2 There is weak evidence from one trial (**Williams 2007 [RCT, USA, +]**) to suggest high dose NRT patches (42mg/day) are well tolerated in schizophrenia and schizoaffective disorder.

ES21.3 There is weak evidence from two trials (**Hartman 1991 [RCT, USA, ++]; Saxon 2003 [NRCT, USA, –]**) to suggest NRT patches (8mg/day are well tolerated in participants with mental health disorders.

Adverse events related to the use of NRT are applicable to the UK setting as there is no reason to assume that this would not be the case.

Unintended consequences

ES27.1 There is very weak evidence from one trial (**Dalack 1999 [NRCT, USA, –]**) to suggest NRT patches (22mg/day) had no detrimental effect on psychiatric symptoms in 10 in-patients with schizophrenia.

ES27.2 There is very weak evidence from one trial (**Dalack 1999 [NRCT, USA, -]**) to suggest NRT patches (22mg/day) increased abnormal involuntary movements in those who used the patch whilst still smoking in 10 in-patients with schizophrenia.

ES27.3 There is very weak evidence from one trial (**Hill 2007 [NRCT, USA, -]**) to suggest NRT patches (14mg/day) had no detrimental effect on psychiatric symptoms in 9 participants with major depression.

Unintended consequences related to the use of NRT are applicable to the UK setting as there is no reason to assume that this would not be the case.

Evidence statements – Varenicline

Effectiveness

ES10.1 There is weak evidence from four trials (**Dutra 2012 [UBA, USA, -]; Panchas 2012 [UBA, USA, -]; Smith 2009 [UBA, USA, -]; Weiner 2011a [RCT, USA, +]**) that varenicline (2mg/day), in predominately outpatients with schizophrenia or schizoaffective disorders, may reduce smoking consumption, where significant reductions were seen in expired CO levels in three studies (**Panchas 2012 [UBA, USA, -]; Smith 2009 [UBA, USA, -]; Weiner 2011a [RCT, USA, +]**); however, no significant difference was seen in continuous abstinence (bio-verified by expired CO) in one trial as compared to placebo (**Weiner 2011a [RCT, USA, +]**).

The evidence from four studies on varenicline is directly applicable to the UK setting as the intervention reflects current clinical prescribing practice in the UK for smoking cessation, and could be feasible within populations with mental health disorders. All of the four studies studies were conducted in the USA.

Adverse events

ES22.1 There is weak evidence from three trials (**Panchas 2012 [UBA, USA, -]; Smith 1999 [UBA, USA, -]; Weiner 2011a [RCT, USA, +]**) to suggest varenicline did not lead to side effects in participants with schizophrenia or schizoaffective disorders; however, side effects were common, relating to nausea and insomnia.

Adverse events related to the use of varenicline are likely to be applicable to the UK setting as there is no reason to assume that this would not be the case.

UNINTENDED CONSEQUENCES

ES28.1 There is weak evidence from four trials (**Dutra 2012 [UBA, USA, -]; Panchas 2012 [UBA, USA, -]; Smith 1999 [UBA, USA, -]; Weiner 2011a [RCT, USA, +]**) to suggest varenicline (2mg/day) had no significant detrimental effect on psychiatric symptoms, cognitive function, or suicide ideation in predominately outpatients with schizophrenia.

Unintended consequences from using varenicline are likely to be applicable to the UK setting as there is no reason to assume that this would not be the case.

EVIDENCE STATEMENTS – BUPROPION WITH NRT

EFFECTIVENESS

ES11.1 There is very weak evidence from one trial (**Saxon 2003 [NRCT, USA, -]**) to suggest the combination of bupropion (300mg/day) and NRT (21mg/day) is effective for reducing smoking consumption and expired CO levels compared to mono-therapy or no pharmacotherapy in 115 psychiatric outpatients in the short term.

ES11.2 There is moderate evidence from a pooled analysis of two trials (**George 2008 [RCT, USA, ++]; Culhane 2008 [RCT, USA, -]**) to suggest the combination of bupropion (300mg/day) and NRT (21mg/day) is effective for smoking cessation in the short term in outpatients with schizophrenia (Pooled OR 9.95, 95% CI 2.15-46.12). However, there is moderate evidence from one trial (**George 2008 [RCT, USA, ++]**) to suggest the combination of bupropion (300mg/day) and NRT (21mg/day) is not effective for smoking cessation in the long term in 59 outpatients with schizophrenia.

The evidence from the studies based on the combination treatment of bupropion with NRT is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. All of the studies were conducted in the USA.

ADVERSE EVENTS

ES23.1 There is very weak evidence from one trial (**Saxon 2003 [NRCT, USA, -]**) to suggest combination treatments of bupropion and NRT patches are well tolerated in major mental health disorders (axis I psychiatric disorders).

Adverse events related to the use of the combination of bupropion with NRT are likely to be applicable to the UK setting as there is no reason why this would not be the case.

UNINTENDED CONSEQUENCES

ES29.1 There is moderate evidence from trial (**George 2008 [RCT, USA, ++]**) to suggest the combination of bupropion (300mg/day) and NRT patches (21mg/day) had no significant effect on psychiatric symptoms in 59 outpatients with schizophrenia.

Unintended consequences from using the combination of bupropion and NRT are likely to be applicable to the UK setting as there is no reason why this would not be the case.

Evidence statement – High Intensity Behavioural Therapy with Bupropion

Effectiveness

ES12.1 There was very weak evidence from one trial (**Weiner 2001 [UBA, USA, -]**) to suggest the combination of high intensity behavioural therapy with bupropion significantly reduced smoking consumption in 9 outpatients with schizophrenia from baseline to short term follow-up (mean expired CO levels reduced from 39.4 to 18.4 ppm).

The evidence from the individual study on the combination of high intensity behavioural therapy with bupropion is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. The study was conducted in the USA.

Unintended consequences

ES30.1 There is very weak evidence (**Weiner 2001 [UBA, USA, -]**) to suggest the combination of high intensity behavioural therapy with bupropion (300mg/day) for smoking reduction has no detrimental effect depression, anxiety, or psychiatric symptoms in 9 outpatients with schizophrenia; however, some evidence of an improvement was seen for alogia.

Unintended consequences from using the combination of high intensity behavioural therapy with bupropion are likely to be applicable to the UK setting as there is no reason why this would not be the case.

Evidence statements – High Intensity Behavioural Therapy with NRT

Effectiveness

ES13.1 There is moderate evidence from one trial of 298 in-patients and outpatients with a diagnosis of non-acute psychotic disorders (**Baker 2006 [RCT, Australia, +]**) to suggest high intensity behavioural therapy (CBT with motivational interviewing) in addition to NRT (21mg/day) resulted in no significant effect on continuous smoking abstinence (bio-verified by CO<10ppm) at short (OR 2.95, 95% CI 0.83-10.53), medium (OR 2.84, 95% CI 0.48-16.67) and long (OR 5.28, 95% CI 0.31-90.20) term follow-ups.

ES13.2 There is weak evidence from two trials in participants with a diagnosis of non-acute psychotic disorders (**Baker 2006 [RCT, Australia, +]; Baker 2009 [NRCT, Australia, -]**) that high intensity (CBT with motivational interviewing) in addition to NRT (21mg/day or up to 42mg/day) reduced self-reported cigarette consumption. In one trial (**Baker 2006 [RCT, Australia, +]**) a 50% or more reduction in cigarette consumption was seen in the short (OR 3.89, 95% CI 1.9-7.89) and long (OR 2.09, 95% CI 1.03-4.27) term, but not at medium term follow-up (OR 1.88, 95% CI 0.92-3.82). In the other trial (**Baker 2009 [NRCT, Australia, -]**) a significant reduction in the number of cigarettes smoked per day was seen from baseline to short term follow-up (mean reduction from 30.8 to 17.2 cigarettes/day).

ES13.3 There is weak evidence from one trial of 322 outpatients with a diagnosis of depression (**Barnett 2008 [RCT, USA, +]**) to suggest high intensity behavioural support in addition to NRT (dose not stated) (and an offer of bupropion in those who continued to smoke) resulted in a higher proportion of participants being abstinent at long term follow-up (7 day point prevalence, bio-verified by CO<10ppm, 24.6% versus 19.1%, p value not reported).

The evidence from the studies on the combination of high intensity behavioural therapy with NRT is directly applicable to the UK setting as the intervention reflects current clinical prescribing practice in the UK for smoking cessation, and could be feasible within populations with mental health disorders. Two of the studies were conducted in Australia which has a similar smoking treatment service to the UK; the remaining study was conducted in the USA.

Unintended consequences

ES31.1 There is very weak evidence from one trial (**Baker 2009 [NRCT, Australia, –]**) to suggest the combination of high intensity behavioural therapy with NRT patches (42mg/day) had no significant effect on psychiatric symptoms or quality of life in 48 outpatients with a non-acute psychotic disorder.

ES31.2 There is weak evidence from one trial (**Baker 2006 [RCT, Australia, +]**) to suggest the combination of high intensity behavioural therapy with NRT (21mg/day) had no significant effect on psychiatric symptoms, quality of life, depression, or anxiety in 298 in-patients an outpatients with schizophrenia.

ES31.3 There is weak evidence from one trial (**Barnett 2008 [RCT, USA, +]**) to suggest the combination of high intensity behavioural therapy with NRT (dose not stated) had no significant effect on depressive symptoms in 322 outpatients with major depression.

Unintended consequences as a result of using the combination of high intensity behavioural therapy with NRT are applicable to the UK setting as there is no reason why this would not be the case.

Evidence statement – Contingency Payments with Bupropion

Effectiveness

ES14.1 There is moderate evidence from one trial (**Tidey 2011 [RCT, USA, ++]**) to suggest contingency payments given in addition to bupropion (300mg/day) did not significantly reduce smoking, or have a detrimental effect on cigarette craving, in 57 outpatients with schizophrenia.

The evidence from the individual study on the combination of contingency payments with bupropion is potentially applicable to the UK as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. The study was conducted in the USA.

UNINTENDED CONSEQUENCES

ES32.1 There is moderate evidence from one trial (**Tidey 2011 [RCT, USA, ++]**) to suggest contingency payments given in addition to bupropion (300mg/day) does not have a detrimental effect on psychiatric symptoms in 57 outpatients with schizophrenia.

Unintended consequences as a result of using the combination of contingency payments with bupropion are likely to be applicable to the UK setting as there is no reason why this would not be the case.

EVIDENCE STATEMENTS – CONTINGENCY PAYMENTS WITH NRT

EFFECTIVENESS

ES15.1 There is very weak mixed evidence from one trial of 180 outpatients with schizophrenia or schizoaffective disorders (**Gallagher 2007 [RCT, USA, -]**) regarding the effectiveness of contingency payments, given in addition to NRT (21mg/day), on abstinence compared to self-quit interventions in the short term and at medium term. Significant increases in smoking cessation were observed when abstinence was bio-verified by CO≤10ppm (short term, OR 13.73, 95% CI 3.85-49.03; medium term, OR 7.87, 95% CI 2.72-22.79). No significant effects were seen when abstinence was bio-verified by saliva cotinine<15ng/ml at short term or medium term follow-up; however, it should be noted that salivary cotinine levels are higher than a non-smokers when NRT patches are used, therefore this is not an optimal method of bio-verification in this instance.

ES15.2 There is very weak evidence from one trial of smoking reduction (**Tidey 2002 [NRCT, USA, -]**) to suggest contingency payments with NRT patches resulted in significantly reduced levels of cigarette/tobacco consumption in 17 outpatients with schizophrenia (measured using expired CO and salivary cotinine levels), but did not have an effect on the anticipation of an immediate positive outcome from smoking or on relief of nicotine withdrawal symptoms.

The evidence from the studies on the combination of contingency payments with NRT is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. Both studies were conducted in the USA.

UNINTENDED CONSEQUENCES

ES33.1 There is very weak evidence from one trial of 180 outpatients with schizophrenia or schizoaffective disorders (**Gallagher 2007 [RCT, USA, -]**) to suggest contingency payments given in addition to NRT (21mg/day) does not have detrimental effects on psychiatric symptoms in the short term and medium term.

Unintended consequences as a result of using the combination of contingency payments with NRT are likely to be applicable to the UK setting as there is no reason why this would not be the case.

ii) How effective are interventions for temporary abstinence in helping people from the populations of interest?

Evidence statement – Temporary Abstinence Interventions

ES16.1 No studies were identified which assessed the effectiveness of interventions for temporary abstinence in people with mental health illness.

- *How does the effectiveness of smoking cessation and temporary abstinence interventions vary by mental health diagnosis, gender, sexual orientation, age, ethnicity, religion, socioeconomic status, disability, and by populations of interest (including patients, household members, visitors and staff)?*

Evidence statement – Progress Plus Criteria

Effectiveness

ES17.1 No studies were identified which assessed the differential effectiveness of smoking cessation interventions by mental health diagnosis, gender, sexual orientation, ethnicity, religion, socioeconomic status, disability, or in populations of interest other than patients (for example, household members, visitors or staff).

ES17.2 There is very weak evidence from one trial (**Brown 2003 [RCT, USA, -]**) to suggest high intensity behavioural therapy with NRT had no overall significant effect on smoking cessation in 191 adolescent psychiatric in-patients at short term and long (OR 1.16, 95% CI 0.59-2.31) term outcome timings.

The evidence from the individual study on high intensity behavioural therapy in adolescents is potentially applicable to the UK as there is no reason to assume that the interventions could not be implemented in UK outpatient and in-patient settings.

- *Are there differences in the effectiveness of smoking cessation and temporary abstinence interventions by deliverer, timing (or point in the care pathway), frequency, duration, and severity of dependence, and setting in which the intervention is assessed, for example in-patients versus out-patient?*

EVIDENCE STATEMENT – TYPE OF PSYCHOTIC MEDICATION

ES18.1 There is weak evidence from one trial (**George 2000 [quasi-RCT, USA, +]**) to suggest the effectiveness of high intensity behavioural therapy for smoking cessation was not significantly related to the type of antipsychotic medication used in schizophrenia.

ES18.2 There is contradictory strong evidence from three trials (**George 2002 [RCT, USA, ++]; Evins 2005 [RCT, USA, ++]; Evins 2007 [RCT, USA, ++]**) regarding the difference in effectiveness of bupropion for smoking cessation by the type of antipsychotic medication used in schizophrenia.

The evidence from the studies is potentially applicable to the UK as the interventions are feasible within the UK setting.

iii) How effective are current strategies/approaches used by secondary care mental health services for identifying and referring people from the population of interest to stop smoking or hospital based stop smoking services?

EVIDENCE STATEMENT

ES34.1 No studies were identified which assessed the effectiveness of current strategies or approaches used by secondary care mental health services for identifying and referring people from the population of interest to stop smoking or hospital based stop smoking services.

iv) How effective are current strategies/approaches used by secondary care mental health services for identifying and providing people from the population of interest with smoking cessation information, advice and support?

EVIDENCE STATEMENTS

ES35.1 No studies were identified which assessed the effectiveness of current strategies or approaches used by secondary care mental health populations for identifying and providing people from the population of interest with smoking cessation information, advice and support.

v) Which strategies/approaches are effective in encouraging mental health care professionals to record smoking status and refer populations of interest to stop smoking services?

EVIDENCE STATEMENTS

ES36.1 No studies were identified which assessed the effectiveness of current strategies or approaches used by secondary care mental health populations for recording smoking status in the population of interest.

ES36.2 No studies were identified which assessed the effectiveness of current strategies or approaches used by secondary care mental health populations for referring populations of interest to stop smoking services.

ES36.3 There is moderate evidence from one trial of 78 outpatients with schizophrenia (**Steinberg 2004 [RCT, USA, ++]**) to suggest that a single session of motivational interviewing resulted in a higher proportion of participants seeking referral for a stop smoking service compared to psycho-educational or brief intervention.

The evidence from the individual study of high intensity behavioural therapy as an intervention to increase referral to a stop smoking service is directly applicable to the UK as the study was based on an outpatient population with mental health disorders, and the intervention is feasible in the UK setting as it is currently used for smoking cessation in the general population. The study was conducted in the USA.

DISCUSSION

This review of smoking cessation in secondary mental health services comprises of a large body of evidence. Fifty-nine studies were identified, of which 10 were based on systematic or critical review methodology, and the remaining 49 were primary evidence which were included in this review. The majority of the studies assessed the effectiveness of interventions in schizophrenia, with only a few studies assessing outcomes in different mental health populations. Most interventions assessed included behavioural therapies, bupropion, NRT, varenicline. The majority of studies were conducted in the United States, with few studies from other countries, and no studies were identified from the UK. The methodological quality of the studies was very variable, with few studies being awarded the highest quality for both internal and external validity. The majority of studies presented smoking abstinence using bio-verification of either expired CO or cotinine levels.

Overall, the evidence from the review suggested:

Behavioural therapy (with no pharmacotherapy)

Very few well conducted high quality studies have been performed to assess the effectiveness of high intensity behavioural therapy for smoking cessation or reduction. However, the evidence to date suggests high intensity behavioural therapy may be effective in populations with specific mental health disorders.

- The effectiveness of high intensity behavioural therapy in people with psychiatric disorders is mixed and mostly based on weak evidence, where an effect was seen in the short term in adults for cessation and smoking reduction, but no effect on cessation was seen in the long term in adolescents. However, there was moderate evidence that integrated tailored behavioural therapy was more effective for smoking cessation in PTSD in the short and long term, than usual standard of care (referral to a specialised smoking cessation clinic)
- There was moderate evidence to suggest high intensity behavioural therapy did not appear to be more effective for smoking cessation than lower intensity behavioural therapy in the short term in schizophrenia on cessation; however, it should be noted that in one of the studies the intensity of the behavioural therapy in the control group was relatively high
- There was moderate evidence to suggest low intensity behavioural therapy was not effective for smoking cessation or reduction in schizophrenia; however, there was very weak evidence to suggest it may be effective for smoking reduction in other psychiatric populations
- There was moderate evidence to suggest motivational interviewing may be effective in increasing the number of people with mental health disorders to seek referral for a stop smoking service compared to psycho-educational or brief intervention.

Bupropion

Several well conducted high quality studies have been performed to assess the effectiveness of bupropion for smoking cessation or reduction. The evidence to date suggests bupropion is effective for smoking cessation in the short term in populations with schizophrenia.

- There was strong evidence that bupropion was effective for increasing smoking cessation in the short term in schizophrenia, but the effect in the medium and long term is unclear
- There was moderate evidence to suggest bupropion was effective for smoking reduction in the short term in schizophrenia
- There was very weak evidence to suggest bupropion did not appear to be effective for smoking cessation in PTSD or bipolar

Nicotine replacement therapy (NRT)

Very few well conducted high quality studies have been performed to assess the effectiveness of NRT for smoking cessation or reduction. The evidence to date is mixed regarding whether NRT is effective in populations with mental health disorders.

- There was weak evidence to suggest high dose NRT may be more effective than standard dose NRT for cessation in schizophrenia

- There was mixed very weak evidence to suggest NRT regarding the effectiveness of NRT for smoking reduction or cessation in major depression or schizophrenia in the short term

VARENICLINE

No well conducted high quality studies have been performed to assess the effectiveness of varenicline for smoking cessation or reduction. The evidence to date suggests varenicline may have some effectiveness for reducing smoking.

- There was weak evidence to suggest varenicline may reduce smoking consumption, but was not effective for abstinence, in schizophrenia

OTHER PHARMACOTHERAPIES

Very few well conducted moderate to high quality studies have been performed to assess the effectiveness of other pharmacotherapies for smoking cessation or reduction. The evidence to date suggests clozapine (an atypical [new generation] antipsychotic medication) may be effective for reducing smoking.

- There was moderate evidence to suggest higher doses of clozapine (350-600mg/day) may be effective for smoking reduction, but no effect was seen for smoking cessation, in schizophrenia.
- There was very weak evidence to suggest fluoxetine did not appear to be effective for smoking reduction in major depression
- There was very weak evidence to suggest galantamine did not appear to be effective for smoking reduction in schizophrenia
- There was moderate evidence to suggest naltrexone was not effective for smoking cessation or reduction in consumption in schizophrenia

COMBINATIONS OF INTERVENTIONS

Very few well conducted high quality studies have been performed to assess the effectiveness of combinations of interventions as compared to control. The evidence to date suggests the combination of bupropion with NRT may be effective for smoking cessation.

- There was very weak evidence to suggest the combination of bupropion with NRT may be effective in reducing smoking consumption in psychiatric populations
- There was moderate evidence to suggest the combination of bupropion with NRT was effective for smoking cessation in the short term, but not in the long term, in schizophrenia
- There was very weak evidence to suggest the combination of high intensity behavioural therapy with bupropion may reduce smoking consumption in schizophrenia
- There was weak evidence to suggest the combination of high intensity behavioural therapy with NRT may be effective for reducing smoking consumption, but had no effect on cessation, in non-acute psychotic disorders or depression

CONTINGENCY PAYMENTS (WITH OR WITHOUT PHARMACOTHERAPIES)

Very few well conducted high quality studies have been performed to assess the effectiveness of contingency payment with or without pharmacotherapies for smoking cessation or reduction. The evidence to date suggests the combination of contingency payments with bupropion was effect for reducing smoking in specific mental health populations.

- There was weak evidence to suggest contingency payments may be effective for reducing smoking consumption in schizophrenia
- There was moderate evidence to suggest contingency payments with bupropion was effective on reducing smoking in schizophrenia
- There was very weak evidence to suggest contingency payments with NRT patches may be effective for a reduction in smoking consumption and smoking abstinence in schizophrenia

EFFECTIVENESS OF INTERVENTION BY TYPE OF ANTI-PSYCHOTIC MEDICATION

There were several well conducted high quality studies that have been performed to assess the difference in effectiveness of interventions for smoking cessation by the type of anti-psychotic medication used. The evidence to date is mixed regarding whether the effectiveness differs between using typical and atypical antipsychotic medication.

- There was mixed moderate evidence regarding the difference in effectiveness of high intensity behavioural therapy or bupropion for smoking cessation by the type of anti-psychotic medication used in schizophrenia.

No studies were identified which assessed:

- The effectiveness of interventions for temporary abstinence in people with mental health illness.
- The effectiveness of current strategies or approaches used by secondary care mental health services for identifying and referring people from the population of interest to stop smoking or hospital based stop smoking services.
- The effectiveness of current strategies or approaches used by secondary care mental health populations for identifying and providing people from the population of interest with smoking cessation information, advice and support.
- The effectiveness of current strategies or approaches used by secondary care mental health populations for referring populations of interest to stop smoking services.

This review highlights the urgent need for further high quality research to be performed in the areas of smoking cessation and smoking reduction in secondary care mental health service settings in the majority of the identified areas, and particularly in the UK.

ABBREVIATIONS USED

BDS/I Beck Depression Scale or Inventory

CBT Cognitive behavioural therapy

CI Confidence Interval

CO Carbon Monoxide

FTND Fagerstrom Test for Nicotine Dependence

NRCT Non-Randomised Controlled Trial

NRT Nicotine Replacement Therapy

OR Odds Ratio

PANSS Positive and Negative Symptoms scale for Schizophrenia

PPM parts per million

PTSD Post-Traumatic Stress Disorder

RCT Randomised Controlled Trial

SR Standard Release (for bupropion)

UBA Uncontrolled Before and After study

INTRODUCTION AND BACKGROUND

SIGNIFICANCE OF SMOKING FOR MENTAL HEALTH

The significance of tobacco smoking in the context of severe mental illness is substantial. Patients diagnosed with severe mental illness are up to three times more likely to be smokers than the general population, with smoking prevalence reaching figures of up to 70% for certain sub groups, such as in-patients, and patients with schizophrenia [1]. Smokers with mental illness have also been found to display patterns of heavy smoking and severe nicotine dependence [2], as well as higher nicotine and cotinine levels that are attributable to increased nicotine intake per cigarette [3]. The disproportionately high rates of smoking have been identified as causes of the increased risk of tobacco-related morbidity and excess mortality in this population (with cancers, respiratory and cardiovascular disease prevalence being high) [4], thus constituting a major contributor to health inequalities in this population. The importance of addressing the issue is increasingly being recognised and has been acknowledged in a range of seminal documents, such as the recent governmental tobacco control plan *Healthy lives, healthy people* (2011), and the mental health strategy plan *No health without mental health* (2011).

The underlying reasons for the strong relationship between smoking and mental illness are complex and vary across diagnoses. Factors contributing to increased smoking have been found to be neurobiological, psychosocial, and genetic in nature [5, 6]. Nicotine interacts with several neurotransmitter systems in the brain and mediates the release of neurotransmitters such as dopamine, noradrenaline and serotonin, which affect mood, cognitive functioning, attention, and memory. Self-medication for and self-regulation of symptoms of mental illness has therefore been proposed as a potential explanation for frequent and heavy smoking among individuals with mental illness [4]. It has also been emphasised that smoking often constitutes a means of social interaction, reducing social inhibition and isolation frequently encountered in this population [5]. Smoking is also relevant from a clinical perspective, as hydrocarbon agents in tobacco smoke induce liver enzymes responsible for drug clearance, thus affecting drug levels of antipsychotic medication. Patients who smoke consequently require higher doses of medication, as their drug metabolism is accelerated by smoking. Hence, tobacco abstinence or quitting requires monitoring of blood levels of medications such as clozapine, as decelerated clearance can potentially lead to toxicity [6].

SMOKING IN MENTAL HEALTH SETTINGS: SYSTEMIC ISSUES

Despite the complexities that mark smoking as a matter of particular importance in the context of mental illness, tobacco dependence constitutes a largely neglected issue in mental health settings, with smoking being historically deeply embedded in the culture of treatment environments [7], and clinicians being reluctant to address the issue proactively as an integral part of treatment [8]. While a societal change towards reducing smoking and the exposure to tobacco smoke in public and work places has taken place in the UK over recent years, smoking is still largely condoned across psychiatric settings, and many mental health professionals perceive it as an important coping mechanism for patients [9]. Smoking has, furthermore, transpired to be a frequently used means of reward or punishment in achieving compliance with treatment, and to play an important part in the context of social interaction between patients and staff [10]. Of particular importance in this context

is the smokefree policy that has been implemented in mental health settings in July 2008. Whilst this is a potential avenue towards health protection and promotion in a vulnerable population, it has since been shown that there is cause for concern, as policies appear to be implemented incoherently, with smoking still being facilitated on a regular basis and viewed as the norm rather than the exception [11]. Furthermore, striking deficiencies in clinical staff knowledge with regard to smoking and its links with mental illness, including metabolic interactions with medication and use of pharmacotherapy for smoking cessation, have been identified, which arguably pose challenges to the appropriate support of patient smokers admitted to treatment environments in which their smoking behaviour is likely to change [12].

TREATMENT OF SMOKING PATIENTS WITH SEVERE MENTAL ILLNESS

Contrary to common perception, patients with severe mental illness are frequently willing to quit smoking [13] provided they receive tailored support, though success in quitting appears to be only half of that in the general population [14], and relapse rates are higher [7]. Pharmacological treatment with both NRT and bupropion (the most recent pharmacological treatment, varenicline, is currently being trialed for safety in the psychiatric population), given separately or in combination, has proven effective and well-tolerated in psychiatric populations [15]. Additional cognitive behavioural support in groups, which has been shown to have potentially beneficial outcomes on quitting attempts in the normal population [16], has been integrated into tailored behavioural programmes for patients with severe mental illness successfully [17]. As many mental health patients are severely dependent on tobacco, and typically experience changing levels of motivation to stop smoking depending on their perceived ability to address their addiction in the light of mental resources, it has been proposed that in this population, smoking reduction may be a viable route towards harm reduction and eventual abstinence [18].

However, clear guidance with regard to treatment models, including the integration of tobacco dependence treatment in care pathways and consideration of smokefree policy implementation in treatment settings, is to date missing. In view of the importance of the issue from public health, clinical, economic, sociological, and policy perspectives, this is a shortcoming that should urgently be addressed.

AIM OF THE REVIEW

To assess the effectiveness of smoking cessation and temporary abstinence interventions in mental health services, including strategies for referring people to stop smoking or hospital based stop smoking services, for the populations of interest.

RESEARCH QUESTIONS ADDRESSED

The review will address the following key research questions:

i) How effective are smoking cessation interventions in helping people from the populations of interest?

ii) How effective are interventions for temporary abstinence in helping people from the populations of interest?

iii) How effective are current strategies/approaches used by secondary care mental health services for identifying and referring people from the population of interest to stop smoking or hospital based stop smoking services?

iv) How effective are current strategies/approaches used by secondary care mental health services for identifying and providing people from the population of interest with smoking cessation information, advice and support?

v) Which strategies/approaches are effective in encouraging mental health care professionals to record smoking status and refer populations of interest to stop smoking services?

Subsidiary questions include:

- *How does the effectiveness of smoking cessation and temporary abstinence interventions vary by mental health diagnosis, gender, sexual orientation, age, ethnicity, religion, socioeconomic status, disability, and by populations of interest (including patients, household members, visitors and staff)?*
- *Are there differences in the effectiveness of smoking cessation and temporary abstinence interventions by deliverer, timing (or point in the care pathway), frequency, duration, and severity of dependence, and setting in which the intervention is assessed, for example in-patients versus out-patient?*
- *What are the adverse events and other consequences associated with using smoking cessation and temporary abstinence interventions in the populations of interest?*

METHODS

INCLUSION AND EXCLUSION CRITERIA

TYPES OF STUDY DESIGNS

We included reviews of reviews, systematic reviews and guidelines (including NICE guidelines), randomised controlled trials, and non-randomised controlled trials. Controlled before and after studies, interrupted time series and uncontrolled before and after studies were also considered for potential relevance.

TYPES OF PARTICIPANTS

We considered studies which include the following populations of interest of any age who smoke:

- All users of secondary care mental health services, including those who are in the process of being referred to or have recently been discharged from child, adolescent, adult or older people mental health services:
  - In-patient, residential and long-term care for severe mental illness in hospitals, psychiatric and specialist units and secure hospitals
  - Patients who are within the care of specialist community-based multidisciplinary mental health teams
- People living in the same household as a mental health service user, such as partners, parents, other family members and carers
- Visitors to secondary care mental health setting who are not receiving treatment or care, such as relatives or friends of patients or service users
- Staff (including support staff, volunteers, agency/locum staff and staff employed by contractors) working in secondary care mental health settings, in particular those who have direct contact with patients and service users

We did not consider users of primary care services, users of secondary care services other than mental health services; and their parents, carers and other family members; staff working in, and visitors to, secondary care services other than mental health.

TYPES OF INTERVENTIONS

ACTIVE INTERVENTIONS:

We included any pharmacological, psychological, behavioural, or self-help intervention that aims to assist with smoking cessation or temporary abstinence. Interventions of relevance included pharmacological interventions, administered alone or in combination with other interventions; psychological interventions, including behavioural support, counselling and advice (with and without a pharmacological intervention); self-help approaches to smoking cessation or temporary abstinence without additional support. Behavioural therapy was categorised into high or low intensity as defined empirically by the included studies; with high intensity therapies typically involving at least

30 minutes of face-to-face contact if only one session was delivered, or at least 20 minutes of face-to-face contact where more than one session was delivered. Psychological and behavioural interventions could include concomitant use of pharmacological interventions to assist with cessation prior to the target quit date; however, in this case, use of pharmacological interventions needed to be equivalent in the active and comparator groups before and after cessation. Similarly, pharmacological interventions could include psychological or behavioural interventions; however, in this case, the type and intensity of support needed to be comparable between the active and comparator groups. Pharmacological interventions not currently licensed for temporary abstinence were also eligible for inclusion. We included any strategies, protocols or systems used by relevant health professionals to help identify smokers, record advice given and refer them to services, alone and share information between different groups of health professionals and across the care pathway.

COMPARATORS:

We included comparisons of interventions with each other (administered alone or in combination), placebo or usual care. Self-help interventions were compared to not using a self-help intervention. Approaches to improve identification, recording of advice and referrals were compared with usual care.

TYPES OF OUTCOME MEASURES

Primary outcomes of interest included the proportion of participants who made successful quit attempts; changes in mean biochemically validated levels of smoking from baseline; and self-reported cigarette consumption. Where studies presented more than one type of abstinence measure, we used prolonged or continuous abstinence in preference to point prevalence abstinence. Additionally, we used biochemical validated abstinence (such as exhaled carbon monoxide or saliva cotinine levels) in preference to self-reported abstinence, where data were available. We included studies which report the follow-up within 10 years of the completion on the intervention.

Other outcomes included an assessment of current strategies using the number of referrals to and contacts with stop smoking services; a comparison of the number of smoking cessation referrals between mental health care and other settings; assessments of improvement in health (for example, recovery rates); changes in recording or referral procedures or care pathway development, following targeted interventions to support the implementation of tobacco treatment services in mental health settings.

Further outcomes of interest included measures of self-efficacy, nicotine dependence and withdrawal, motivation, confidence, where these were reported in addition to assessing smoking cessation ascertained as described above. We additionally assessed the proportion of populations of interest with adverse events.

EXCLUSION CRITERIA

We did not consider smoking cessation or temporary abstinence interventions in primary care, medical and surgical care or obstetric care. We also did not consider policy or legislative interventions, or interventions aimed at preventing of uptake of tobacco use. We additionally excluded studies assessing the effectiveness of interventions in substance abuse (drug and alcohol).

SEARCH STRATEGY

Sensitive search strategies were developed by an information specialist in conjunction with the research team and peer-reviewed by information specialists at NICE using a combination of controlled vocabulary and free-text terms. The search strategy was initially developed in MEDLINE and was then adapted to meet the syntax and character restrictions of each included database.

The ICD-10 Classification of Mental health and Behavioural Disorders diagnostic criteria was used to refine the populations of interest to aid with searching for relevant disorders. The search strategy focused on the following ICD-10 diagnoses, for each of which we developed detailed search terms as demonstrated in the example of the search strategy:

F00-F09	Organic, including symptomatic, mental disorders
F10-F19	Mental and behavioural disorders due to psychoactive substance use
F20-F29	Schizophrenia, schizotypal and delusional disorders
F30-F39	Mood (affective) disorders
F40-F48	Neurotic, stress-related and somatoform disorders
F50	Eating disorders
F60-F62	Specific personality disorders, Mixed and other personality disorders, Enduring personality changes
F84	Pervasive developmental disorders
F90-F92	Hyperkinetic disorder, Conduct disorder, Mixed disorders of conduct and emotions

In our judgement, the search for specific terms related to the following diagnoses would not yield meaningful outcomes (owing to the fact that the respective populations are highly unlikely to constitute target groups of tobacco related research), therefore we did not to develop detailed search terms for those, but to imply inclusion of these groups through the identification of studies that include populations of 'smokers treated in mental health settings' more generically.

F51-F59 The excluded syndromes refer to nonorganic sleep disorders, sexual dysfunction (not caused by organic disorder or disease), mental and behavioural disorders associated with the puerperium, and abuse of non-dependence-producing substances

F63-F69 The excluded disorders refer to habit and impulse disorders, gender identity disorders, disorders of sexual preference, and psychological and behavioural disorders associated with sexual development and orientation

F70-F79 The excluded diagnoses refer to mental retardation

F80-F89 The excluded disorders refer to specific developmental disorders of speech and language, scholastic skills, motor function (excluding F84)

F93-F99 The excluded disorders refer to emotional disorders, social functioning, nonorganic enuresis and nonorganic encopresis with onsets specific to childhood, and tic disorders

Literature searches were conducted from 1985 onwards. The full search strategies for each database source can be found in Appendix 1. The following databases were searched:

- AMED (Allied and Complementary Medicine)
- ASSIA (Applied Social Science Index and Abstracts)
- British Nursing Index
- CDC Smoking & Health Resource Library database
- CINAHL (Cumulative Index of Nursing and Allied Health Literature)
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Tobacco Addiction group Specialist Register
- Conference Papers Index (years: 2008-2012)
- Database of Abstracts of Reviews of Effectiveness (DARE; 'other reviews' in CDSR database)
- Database of Promoting Health Effectiveness Reviews (EPPI Centre DoPHER)
- EMBASE
- Health Evidence Canada
- Health Technology Assessment (HTA) database in the CDSR database
- HMIC
- International Bibliography of Social Sciences
- Medline, including Medline in Process
- PsycINFO
- Social Policy and Practice
- Social Science Citation Index and Conference Proceedings Citation Index
- Sociological Abstracts
- Trials Register of Promoting Health Interventions (EPPI Centre TRoPHI)
- UK Clinical Research Network Portfolio Database

The following websites were also searched for research papers relevant to the review questions:

- Smoke free http://smokefree.nhs.uk
- NHS Centre for Smoking Cessation and Training http://www.ncsct.co.uk/
- Action on Smoking and Health (ASH) http://www.ash.org.uk
- Treat tobacco.net http://www.treatobacco.net/en/index.php
- Society for Research on Nicotine and Tobacco http://www.srnt.org
- International Union against Cancer http://www.uicc.org
- WHO Tobacco Free Initiative (TIF) http://www.who.int/tobacco/en
- International Tobacco Control Policy Evaluation Project http://www.itcproject.org
- Tobacco Harm Reduction http://www.tobaccoharmreduction.org/index.htm
- Current controlled trials www.controlled-trials.com
- Association for the treatment of tobacco use and dependence (ATTUD) www.attud.org
- National Institute on drug abuse- the science of drug abuse and addiction http://www.nida.nih.gov/nidahome.html
- NICE http://www.nice.org.uk/
- Public health observatories http://www.apho.org.uk/resource/advanced.aspx
- Scottish Government http://www.scotland.gov.uk/topics/research
- Welsh Assembly Government http://wales.gov.uk/
- NHS Evidence https://www.evidence.nhs.uk/
- Joseph Rowntree Foundation http://www.jrf.org.uk/publications
- UK Centre for Tobacco Control Studies http://www.ukctcs.org/ukctcs/index.aspx

We electronically searched the World Conference on Tobacco or Health proceedings in years 2006, 2009 and 2012 (the conference is held every three years) to identify further potentially eligible papers, as this conference is not included in the databases and websites above. We also checked reference lists of included previous reviews to identify further potentially eligible studies. Additionally, we screened the electronic files of papers identified from Reviews 1, 2, 3, 6, and 7 for studies that had potential relevance.

Studies were managed during the review using the EPPI-Centre's online review software EPPI-Reviewer (version 4.0).

TITLE AND ABSTRACT SCREENING

All records from the searches were uploaded into a database and duplicate records were removed. Where no abstract was available, a web search was first undertaken to locate one; if no abstract could be found, records were screened on title alone and full-text documents were retrieved where there was any doubt.

To trial the inclusion criteria, a pilot round of screening was conducted on a random selection of 30 document titles and abstracts. Piloting was conducted by three reviewers. A reconciliation meeting was then held to discuss disagreements and suggest changes to the inclusion criteria.

Following the pilot screening, 1,143 records (10%) were double screened. The inter-rater agreement rate for double-screening was 97.7%, which was considered by the project team and NICE to be sufficiently high. As such, the remaining documents were split between two reviewers who independently screened their allocated records. Of the double-screened items, any disagreements were resolved by a third reviewer. Throughout the entire process, the reviewers discussed difficult and ambiguous records to ensure consistency.

The final inclusion criteria are presented below (also see Appendix 2 for detailed guidance and definitions used for each criterion). The criteria were applied in a hierarchical fashion.

- The document must be published during or after 1985
- The document must report on a piece of empirical research
- The title and/or abstract must refer to smoking cessation interventions/ services
- The study (or a component of it) must be conducted in a mental health secondary care setting, or include patients or workers in mental health services, or family/friends/visitors of mental health patients.
- The study design must involve a comparison (e.g., controlled trials, before-and-after) and/or views or process evaluation (e.g., interviews, surveys)

If the study met the above criteria and evaluated the effectiveness of an intervention, it was marked as relevant to Review 4. If the study met the above criteria and included evidence on barriers or facilitators (including knowledge, attitudes and beliefs) of using or implementing smoking cessation interventions/ services, it was marked as relevant to Review 5.

Full text screening

Once all of the titles and abstracts were screened, the full-text documents were retrieved for those records marked for inclusion. The retrieved documents were then re-screened on the basis of the detail available in the full-text article by Ms Jayes using a previously piloted screening checklist (Appendix 3). A random selection of a minimum of 30% of the full-text documents was double-screened by the Ms Jayes and Dr Leonardi-Bee. The first 134 articles were double screened based on full text, and we reviewers agreed on 94%, which was deemed sufficiently high. Any disagreements

were discussed and, if necessary, resolved by Dr Ratschen. Those documents that passed the inclusion criteria on the basis of the full-text screening were included in the review.

Data extraction and quality assessment

Data extraction and appraisal of the quality of the included studies was performed by Dr Leonardi-Bee, with a random selection of 10% being double-assessed by Professor McNeill. Data were extracted using previously piloted data extraction forms which followed the methods as outlined in the methods manual www.nice.org.uk/phmethods2009, and PROGRESS-Plus criteria (age, sex, sexual orientation, disability, ethnicity, religion, place of residence, occupation, education, socioeconomic position and social capital) was noted. Any difference in assignment of quality was resolved through discussion. Internal and external validity of the studies was rated using the previously piloted quality appraisal checklists which followed the methods as outlines in the methods manual, with each study being coded as either ++, +, or -. ++ indicated a high quality score for internal and external validity, where the study demonstrated all or most of the checklist criteria had been fulfilled, and where these had not been fulfilled, the conclusions of the study were unlikely to alter, had this been the case. + indicated moderate quality for internal and external validity, where the study demonstrated some of the checklist criteria had been fulfilled, and where they had not been fulfilled, or not adequately described, the conclusions of the study were unlikely to alter. – indicated a low quality score for internal and external validity, where the study demonstrated few or none of the checklist criteria had been fulfilled and the conclusions of the study were likely or very likely to alter, had this been the case. Composite inter-rater agreement (the per cent agreement) was calculated and reported.

Data synthesis

The results from the studies were expressed as odds ratios (OR) with 95% confidence intervals (CI) for dichotomous outcomes; or as mean differences (MD) with 95% CIs for continuous outcomes. Where raw data were extracted which contained zero cells, to enable estimation of odds ratios, 1 was added to each cell of the 2x2 table. Where possible, we performed random effects meta-analysis to estimate weighted intervention effects across studies, and presented results using forest plots. For psychological interventions, we anticipated using technique-based meta-regression methods to classify interventions into component techniques; however, due to insufficient number of comparable studies this was not performed. Where there were insufficient studies to perform a meta-analysis, studies were described individually.

Timing of outcome measures

The timing of the follow-ups were grouped into categories to reflect the impact of the intervention at different time points; temporary (during a stay or visit at a mental health care setting), short term (outcome closest to 1 month, permitted range 1-5 months), medium term (outcome closest to 6 months, permitted range 6-11 months), long term (outcome closest to 12 months, permitted range 12-23 months), and elongated terms (outcome closest to 5 years, permitted range 2 to 10 years).

ASSESSMENT OF HETEROGENEITY

Statistical heterogeneity was quantified using recognised methods (I^2).

ANALYSES TO EXPLORE REASONS FOR HETEROGENEITY

We anticipated using subgroup and sensitivity analyses and meta-regression to explore heterogeneity, for example based on class of pharmacological intervention, methodological quality, study design, length of the intervention, type and intensity of psychological intervention, measure of abstinence and validation of abstinence; but insufficient numbers of comparable studies were included in the review, thus further analysis was not permissible.

We anticipated using further subgroup analysis to assess the impact of the interventions on the gender, sexual orientation, age, ethnicity, religion, socioeconomic status, mental health diagnosis, disability, and population of interest (including patients, household members, visitors and staff); and whether the intervention varied by deliverer, timing (or point in the care pathway), frequency, duration, and severity of dependence, and setting in which the intervention was assessed, for example in-patients versus out-patient, however, this assessment was limited due to insufficient number of comparable studies.

METHODS FOR DEALING WITH MISSING DATA

Where participant drop-out lead to missing outcome data, we attempted to perform an intention-to-treat analysis using the Russell Standard.

ASSESSMENTS OF PUBLICATION BIAS

Due to insufficient numbers of comparable studies we were unable to perform funnel plots to assess publication bias (small study bias).

ADVERSE EVENT OUTCOMES

Data relating to adverse events were described qualitatively.

SOFTWARE

Data were analysed using Review Manager (version 5.1).

EVIDENCE TABLES

Evidence tables were completed for each included study.

EVIDENCE STATEMENTS

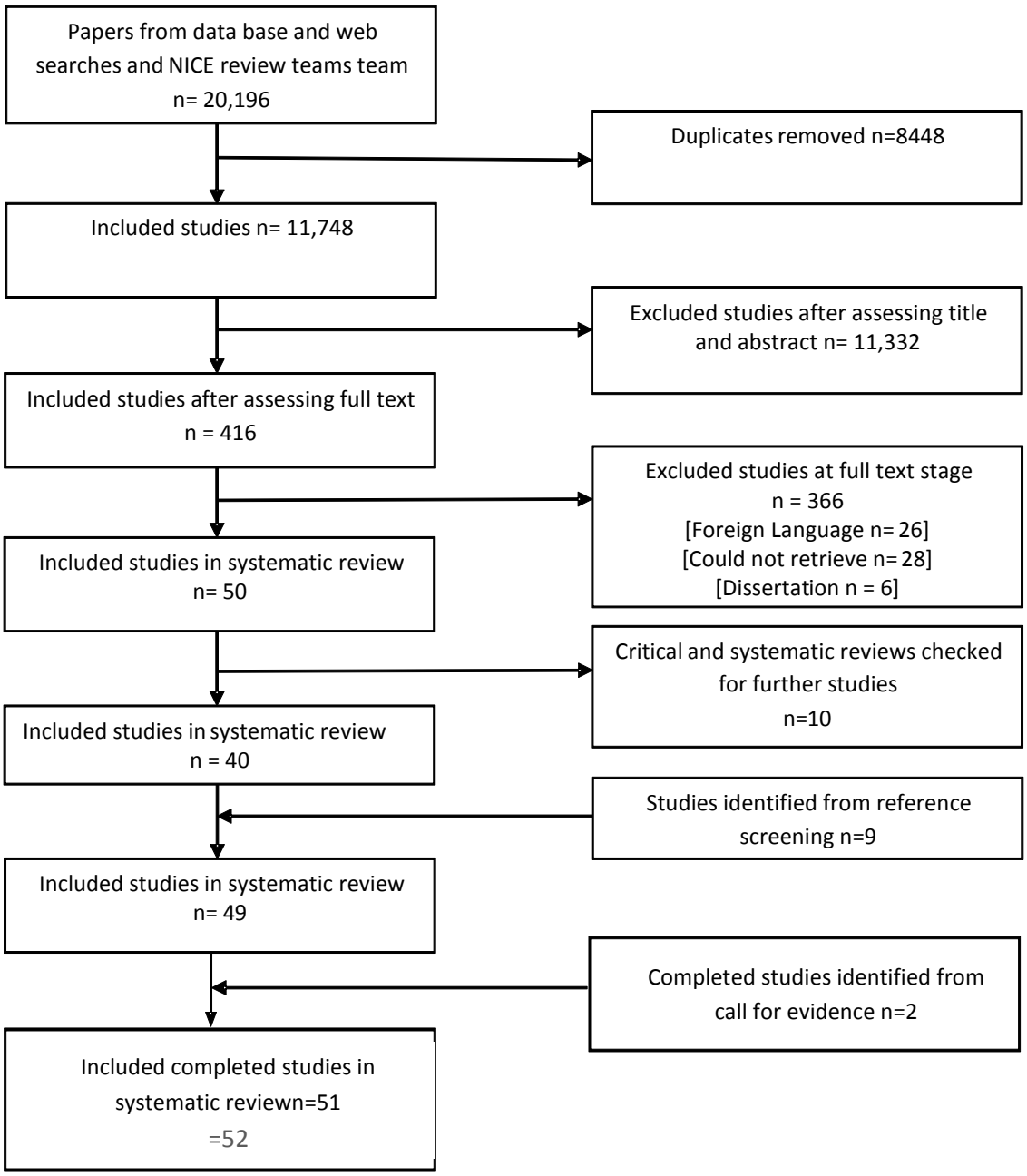
Evidence statements based on an aggregated summary of the available evidence were produced, which reflected the strength (quality, quantity and consistency) of the evidence and statements regarding its applicability were made. The quality of the evidence was categorised as strong (where statements were based on evidence from several high quality studies), moderate (where statements were based on evidence from either one high study, or a mixture of high and lower quality studies), weak (where statements were based on evidence from lower quality studies), or very weak (where statements were based on evidence from individual lower quality studies). Statements were also made where there is a lack of evidence. Statements regarding the applicability of the evidence to the UK setting were also reported and categorised as directly applicable, potentially applicable, or not applicable.

RESULTS

OVERVIEW OF RESULTS FROM SEARCH

20,196 references were identified from the search strategy, comprising of 20,058 references from the databases searched, 35 references located through web searches, and 103 references located through other NICE review teams. Following removal of 8,448 references due to duplication, a total of 11,748 references were screened based on their title and abstract. Of these, 11,332 references were deemed not eligible for inclusion, thus a total of 416 were screened based on their full text. We excluded a total of 366 of the full-text papers with the majority being excluded due to not fulfilling the inclusion criteria; however 26 of these were excluded due to translations not being available, 6 due to the dissertation not being available and 28 due to the full text paper being irretrievable. 10 papers were excluded from the review due to being systematic reviews or critical reviews; however, the reference lists of these reviews were screened for further studies. Additionally, we identified a further 9 eligible papers from reference scanning of identified reviews. A high inter-rater agreement rate of 83% was found between the reviewer based on data extraction and quality assessment. Following the call for evidence, we identified two further studies assessing varenicline for smoking cessation in patients with schizophrenia, and one ongoing randomised placebo-controlled multicenter trial assessing the safety and efficacy of 1mg varenicline (twice per day) given for 12 weeks for smoking cessation in 525 adult smokers with either a current or past diagnosis of major depressive disorder without psychotic features (ClinicalTrials.gov identifier: NCT01078298, sponsor Pfizer). The study was due to complete in June 2012; however, no findings from this study have been presented or published yet. Thus a total of 51 completed studies were deemed eligible for inclusion into the review (Figure 1).

Figure 1 **Flow chart of study selection**



Overview of systematic studies identified from the search

Ten studies identified from the searches used a systematic or critical review methodology (Appendix 4), with the majority of these focusing on interventions for smoking cessation in people with schizophrenia (Bradshaw 2005, Ferron 2009, Tsio 2010a, Tsio 2010b, El-Guebaly 2002, Kisely 2008). Three focused on depression and mood disorders (El-Guebaly 2002, Hitsman 2003, Kisely 2008), and four focused on any non-organic psychiatric disorders and other disorders (Banham 2010, Heckman 2010, Bryant 2011, Kisely 2008). A summary of the reviews are presented in Appendix 5. However, because the reviews were published several years ago, and the papers included in the reviews were also identified from the search strategy, we elected to focus on presenting evidence from individual studies rather than the summarised findings from the reviews. Thus, the reviews below are not presented using evidence tables.

Overview of primary evidence studies included in the review

A total of 51 primary studies were included in the review (Appendix 6), with the majority focusing on interventions for smoking cessation in people with schizophrenia. The remaining studies assessed interventions for smoking cessation in people with post-traumatic stress disorder (PTSD) (3 studies), bipolar (1 study), major depression (4 studies), or encompassed a range of mental health disorders (10 studies).

Settings of the studies

The majority of the included studies were conducted in outpatient (community) mental health populations (32 studies), with only 10 conducted in in-patients mental health populations and three conducted in both in-patient and outpatients. Six further studies were unclear with regard to their populations. Most of the studies recruited participants directly from the users of particular outpatient or in-patient mental health care clinics. The majority of the included studies were conducted in the United States (41 studies), with only a small number being conducted elsewhere in the world (Australia [3 studies], Canada [1 study], China [2 studies], Iran [1 study], Israel [1 study], Poland [1 study], and Taiwan [1 study]). The sample sizes of the included studies varied from 5 to 943. One study failed to report the sample size of the two RCTs included in the report (Culhane 2008).

Interventions assessed

A wide range of single interventions and combinations of interventions for smoking cessation were assessed within the studies, and included behavioural and pharmacotherapies given singularly or in combination. The most commonly used interventions for the smoking cessation trials were behavioural therapy (high intensity, 11 studies; low intensity, 2 studies), nicotine replacement therapy (6 studies), bupropion (10 studies), clozapine (3 studies), or NRT with behavioural therapy (3 studies), combination of NRT with bupropion (3 studies), and four studies were identified which assessed the effectiveness of varenicline. Individual studies assessed the effectiveness of contingency payments; fluoxetine, galantamine, naltrexone, contingency payments with bupropion, contingency payments with NRT. The interventions assessed for smoking reduction were bupropion

(1 study), bupropion with behavioural therapy (1 study), and contingency payment with NRT (1 study).

DESIGNS OF THE STUDIES

The majority of studies used a parallel group RCT design (35 studies); however, a small number of studies used designs based on a quasi-randomised trial (2 studies); a non-randomised trial (2 studies), cross-over design trial (4 studies), randomised before and after trial (1 study), or a non-randomised before and after trial (6 studies), or described the study as an interrupted time series design (1 study, this study appeared to be a RCT from the methods section of the paper).

OUTCOMES ASSESSED

All of the included studies assessed smoking cessation as self-reported quit, with most bio-verification of smoking status either using expired CO, and/or saliva and/or urinary cotinine levels. However, different cut-off levels were used in the studies to determine bio-verified cessation; with the majority using an expired CO level ≤10ppm, whilst others commonly used ≤8ppm. Most of the successful quit attempts were assessed either short term (1-5 months post quit date) or medium term (6-11 months post quit date), with few assessing long term (12-23 months post quit date), and none assessing elongated term (2-10 years post quit date). A few studies reported temporary smoking status (during a stay or visit at a mental health care setting).

One study assessed the effectiveness of interventions for referring the population of interest to a stop smoking or hospital based stop smoking service. None of the studies included in the review assessed the effectiveness of current strategies used by secondary care mental health services for identifying, documenting smoking status and advice given, or the effectiveness of integrating smoking cessation support within care pathways to provide collaborative services across community, primary, mental health care providers. However, information on the barriers and facilitators affecting these outcomes are presented in the Barriers and Facilitators review (R5).

Other outcome measures assessed and included were the number of cigarettes smoked per day, either collected using self-report or the study researcher counting the number of cigarette butts. A wide range of treatment-related outcomes were assessed and included psychiatric symptoms, anxiety, depression, cognitive function, and quality of life measures.

QUALITY ASSESSMENT

The overall quality of the included studies varied, with 10 (20%) and 12 (24%) being awarded the highest quality score for internal and external validity, respectively; which indicated that the study demonstrated all or most of the checklist criteria had been fulfilled, and where these had not been fulfilled, the conclusions of the study were unlikely to alter, had this been the case. 18 (35%) and 26 (51%) were awarded medium quality score for internal and external validity, respectively; which indicated that the study demonstrated some of the checklist criteria had been fulfilled, and where they had not been fulfilled, or not adequately described, the conclusion of the study were unlikely to alter. Finally, 23 (45%) and 13 (25%) were awarded the lowest quality score for internal and external

validity, respectively; which indicated that few or none of the checklist criteria had been fulfilled and the conclusions of the study were likely or very likely to alter, had this been the case.

QUESTION 1A. HOW EFFECTIVE ARE SMOKING CESSATION INTERVENTIONS IN HELPING PEOPLE FROM THE POPULATION OF INTEREST?

46 primary studies were identified and included in the review which addressed this question. These studies are summarised in details in the evidence tables in Appendix 7. The findings from these studies are presented below and structured based on the type of intervention assessed, followed by the population of interest. The study design, country and internal validity quality score for each study is presented in parentheses following the citation.

BEHAVIOURAL THERAPY INTERVENTIONS

HIGH INTENSITY BEHAVIOURAL THERAPY INTERVENTIONS

Brown 2003 (RCT, USA, +) A RCT was conducted that assessed the effectiveness of motivational interviewing in 191 psychiatric in-patients aged 13-17 years who smoked at least one cigarette per week. Eligible diagnoses included mood (n=84), anxiety (n=105), disruptive behaviour (n=150), and substance related (n=136) disorders (participants could have dual disorders); however, participants with current psychotic disorders were excluded. Participants were randomised to motivational interviewing or brief advice. The motivational interviewing group received two 45-minute individual therapy sessions during hospitalisation, and following discharge they were offered NRT patches if they desired to quit smoking and smoked 10+ cigarettes per day. The brief advice group received 5-10 minutes of smoking cessation advice by the study therapist and a self-help pamphlet, and following discharge they were also offered NRT patches if they desired to quit and smoked 10+ cigarettes per day.

SMOKING CESSATION OUTCOMES

The study demonstrated no significant difference between the treatment groups on the number of cigarettes smoked per day at 12 months follow-up (p=0.74). Additionally, 7 day point prevalence (bio-verified with expired CO<10ppm and saliva cotinine<15ng/ml) was not significantly difference at one month (11.0% versus 11.0%), 6 months (13.3% versus 8.5%), or 12 months (14.0% versus 9.9%) follow-up (all p>0.30). Over the 12 month follow-up, no significant difference was seen in the odds of abstinence between the treatment groups (OR 1.16, 95% CI 0.59-2.31; p=0.38); however, the study reported having an anxiety disorder was associated with a higher odds of abstinence (OR 4.71, 95% CI 2.19-10.12; p=0.0001). On discharge, participants in the motivational interviewing group had significantly higher self-efficacy (confidence in ability to refrain from smoking) compared to those receiving brief advice (p=0.04).

Currie 2008 (quasi-RCT, Canada, +) A quasi-RCT was conducted which compared the effectiveness of 8 sessions of a smoking cessation programme as compared to only using 4 sessions in 85 out-patients participants with severe and persistent mental illness who had an interest in

quitting smoking. Both treatment groups used the same smoking cessation programme which was based on popular treatment protocol "Freedom from smoking" particularly tailored for persons with mental illness; participants were randomised to receive either the 4 session version or the 8 session version. The target quit dates was session 3 for the 4 session version, and session 4 for the 8 session version. All participants were encouraged to use NRT gum or patches.

SMOKING CESSATION OUTCOMES

The study reported 7 day point prevalence abstinence, bio-verified by expired CO, was higher in the 8 session version than the 4 session version at each time points (post-treatment, 13% versus 21%; 3 months, 15% versus 24%; 6 months, 8% versus 29%; 12 months, 21% versus 27%; no p values could be determined for the comparisons). Additionally, the study reported post-treatment 7 day point prevalence was higher in makes than females (69% versus 31%, p<0.01).

Kisely 2003 (NRCT, Australia, -) A non-randomised cross-over design study was conducted to assess the effectiveness of behavioural group therapy as compared to no intervention in an outpatient mental health population who were asked to set initial and long term goals for smoking reduction and cessation. Following baseline measurements, all participants initially received a control phase of no intervention for 8 weeks while they were on a waiting list. The intervention phase was then conducted over the next 8 weeks, which comprised of 8 weekly 1.5 hour sessions, where the intervention was conducted by a psychologist and an additional facilitator as needed. The content of the early sessions focused on developing knowledge and motivation surrounding the positive and negative effects of smoking, including short and long term benefits of stopping; with subsequent sessions covering different methods for stopping, dealing with difficult situations, relapse prevention and a smoke-free lifestyle, using CBT methods. Thirty-eight participants were recruited who had a range of mental health outcomes including schizophrenia (n=17), mood disorders (n=16), organic mental health disorder (n=4) or personality disorder (n=1).

SMOKING CESSATION OUTCOMES

The findings from the study demonstrated smoking at 8 weeks follow up, ascertained using case notes, was significantly more likely at the end of the control period than at the end of the intervention period (control, 19/19 versus intervention, 14/19; p=0.02). Half of the participants (n=10) from the cross-over trial were followed-up to three months, at which only 3 participants continued to smoke (p<0.05). The study also demonstrated at the end of the 8 weeks intervention period as compared to the control period significantly lower cotinine levels (p=0.046) and significantly lower FTND scores (p=0.002).

Morris 2011 (RCT, USA, +) A randomised controlled pilot trial was conducted to assess the effectiveness of a tobacco cessation group in addition to a quit-line service in 123 outpatients with psychiatric diagnoses who were interested in quitting regardless of their motivational readiness to quit. Participants were randomised to receive up to 10 sessions of a community based tobacco cessation group facilitated by mental health clinicians with group therapy experience in addition to a

quit-line service, or the quit-line service only. The quit-line service comprised of 5 proactive telephone calls to assist with quitting, promote healthier lifestyles and prevent relapse. All participants were entitled to up to 12 weeks of free NRT patches (21mg/day for weeks 1-6, 14mg/day for weeks 7-8, 7mg/day for weeks 9-12); however, no information was given in the paper regarding usage. The quit-line was facilitated by counsellors who were trained to assist participants with psychiatric disorders.

SMOKING CESSATION OUTCOMES

The study demonstrated participants who had received the group therapy in addition to the quit-line were significantly more likely to achieve 50% reduction in the self-reported number of cigarettes smoked per day at 6 months compared to those who solely received the quit-line (21% versus 8%; Adjusted OR 3.16, 95% CI 1.04-9.65; p=0.045).

McFall 2005 (RCT, USA, +) A RCT was conducted to assess the effectiveness of integrated care in 66 outpatients under treatment for PTSD. Participants were randomised to integrated care or usual standard of care. The integrated care comprised of 5 individual behavioural counselling sessions once a week on a weekly basis (lasting approximately 20 minutes each) and one follow-up contact. The counselling components included education about the health risks of smoking and the benefits of quitting, motivational interventions, coping strategies, and self-help reading materials. The counselling was administered by PTSD clinic prescribers and case managers. The control group received usual standard of care in which they were referred to a smoking cessation clinic, where the participant could attend one group orientation class, followed by individual sessions in which they received medications and behavioural counselling. All participants included in the trial could access the usual standard of care offered to the control group. However, the participants in the control group received no tobacco-cessation interventions from their PTSD clinic providers.

SMOKING CESSATION OUTCOMES

This study demonstrated at each assessment time (2, 4, 6 and 9 months follow-up), participants receiving integrated care were significantly more likely to be abstinent (7 day point prevalence) compared to participants receiving standard care (OR 5.23, 95% CI 1.76 to 15.54; p<0.002).

McFall 2010 (RCT, USA, ++) A RCT was conducted to assess the effectiveness of integrated care in 943 outpatients under PTSD care. All participants had PTSD related to military service. Participants were randomised to integrated care or usual standard of care. The integrated care comprised of 5 weekly individual tobacco cessation therapy sessions which focused on tobacco use education, behavioural skills for quitting, and relapse prevention. These core sessions were then followed by three follow-up visits for those who continued to smoke, and booster sessions could be administered monthly if needed. The control group received usual standard of care in which they were referred to a specialised cessation clinic, and treatment was received within 6 weeks of the referral and smoking cessation medication were prescribed either directly by the clinic staff or through the participant's general practitioner.

SMOKING CESSATION OUTCOMES

The study demonstrated bio-verified point prevalence at 6 months follow-up was significantly higher in the integrated care group compared to the usual standard care group (7 day point prevalence, 78/472 versus 34/471, p<0.001; 30 day point prevalence, 65/472 versus 28/471, p=0.001). Self-reported prolonged abstinence bio-verified by expired CO at 12 months follow-up was significantly more likely in the integrated care group compared to the usual standard care group (Adjusted OR 2.26, 95% CI 1.30 – 3.91). The treatment effect was reported to be consistent across all subgroups considered. At 18 months follow-up, bio-verified point prevalence abstinence was significantly more likely in the integrated care group compared to the usual standard care group (7 day point prevalence, 86/472 versus 51/471, p<0.001; 30 day point prevalence, 80/472 versus 44/471, p<0.001).

Chen 2002 (RCT, China, -) A RCT was conducted to assess the effectiveness of a high intensity behavioural therapy programmes on changes in health beliefs of smoking cessation in 65 outpatients diagnosed with schizophrenia or schizoaffective disorders. Participants were randomised to either a closed smoking cessation programme, consisting of 2 sessions per week for 4 weeks (duration of 1 hour each), or a control group which received no intervention. The smoking cessation programmes focused on information, motivation, strategy, and maintenance.

SMOKING CESSATION OUTCOMES

The study demonstrated 8% and 16% 7 day point prevalence quit rates in the smoking cessation programme group at week 4 and week 8. Insufficient details were given regarding the quit rates of the control group.

George 2000 (quasi-RCT, USA, +) A quasi-RCT was conducted to assess the effectiveness of a specialised schizophrenia group therapy programme as compared to a standard therapy programme in 45 participants with schizophrenia or schizoaffective disorders who were motivated to quit smoking. All participants were given nicotine replacement therapy patches (21mg/24hr) for 6 weeks starting on the target quit date (week 3), decreasing to 14mg weeks 7-10, and 7mg weeks 11 and 12. The intervention group received weekly group therapy for 10 weeks, which was based on 3 weeks of motivational enhancement therapy, followed by 7 weeks of psycho-education, social skills training, and relapse prevention strategies. The control group received 7 weeks of manualised behaviour group therapy and supportive group counselling during the 3 remaining weekly group sessions, with each session lasting 60 minutes.

SMOKING CESSATION OUTCOMES

A borderline significant difference was detected for continuous abstinence (weeks 8-12, with expired CO bio-verification) in favour of the specialised schizophrenia group therapy (32.1% versus 23.5%; p=0.06). However, at 6 months follow-up a significantly greater proportion of participants in the standard therapy program were likely to be abstinent (point prevalence) than compared to the

specialised therapy group (17.6% versus 10.7%; p<0.03). Analysis of weekly expired CO levels demonstrated similar findings.

Williams 2010 (RCT, USA, +) A RCT was conducted to assess the effectiveness of a high intensity behavioural counselling programme in 100 outpatients diagnosed with schizophrenia or schizoaffective disorders, who were motivated to quit smoking. Participants were randomised to one of two high intensity programmes, the study labeled these as 'high intensity' and 'medium intensity'; however, both can be regarded as high intensity as defined by this review in the methods section. For ease, we have elected to use the labels as reported in the paper. The high intensity programme consisted of 24 sessions (45 minute duration each), whereas the medium intensity programme consisted of nine sessions (20 minute duration each); both were given over 26 weeks. The high intensity treatment comprised of a blended approach of motivational interviewing skills and CBT relating to social skills training and relapse prevention, and education relating to NRT. The medium intensity programme focused on smoking cessation, compliance with medication and education relating to NRT, monitoring psychiatric symptoms and education relating to interactions between psychiatric medications and tobacco. Target quit date was during week 5, from which all participants received NRT patches (21mg for 12 weeks, reducing to 14mg for 4 weeks) for 16 weeks.

SMOKING CESSATION OUTCOMES

The study demonstrated no significant difference in continuous abstinence (bio-verified by CO) at 12 weeks after target quit date between the high intensity and medium intensity programmes (15.6% versus 26.2%; p=0.22). Similar non-significant findings were seen at 26 weeks post target quit date (p=0.67) and at one year (p=0.78). No significant differences were seen from baseline to week 12 post target quit date between the high and medium intensity programmes for CO reduction (p=0.76) or the number of cigarettes smoked per day (p=0.35). A survival analysis assessing the time to first cigarette lapse was not significantly difference between the high and medium intensity programmes in a subset of 69 participants (mean 5.1 versus 6.3 days; p=0.32).

Wojtyna 2009 (NRCT, Poland, -)A non randomised pilot trial was conducted to assess the effectiveness of CBT in 44 heavy smoking in-patients who had a diagnosis of schizophrenia or depression. Participants received CBT or educational training for 12 weeks. The CBT group received 2 hour weekly therapeutic sessions which focused on enhancing self-esteem and weekly sessions on educational training. The study was reported in abstract format, with little details given about the interventions.

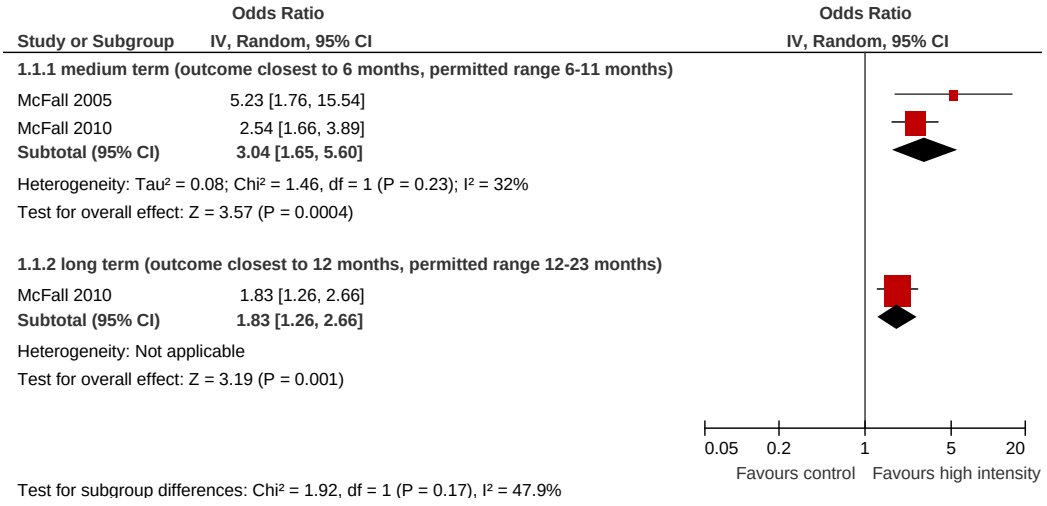
SMOKING CESSATION OUTCOMES

The study demonstrated participants in the CBT group were significantly more likely to report stopping smoking compared to the education training only group (OR 3.64, 95% CI 1.04-12.80; p=0.04). After treatment was completed, the study reported the CBT group smoked less than the education training only group.

META- ANALYSES OF HIGH INTENSITY BEHAVIOURAL THERAPY INTERVENTIONS

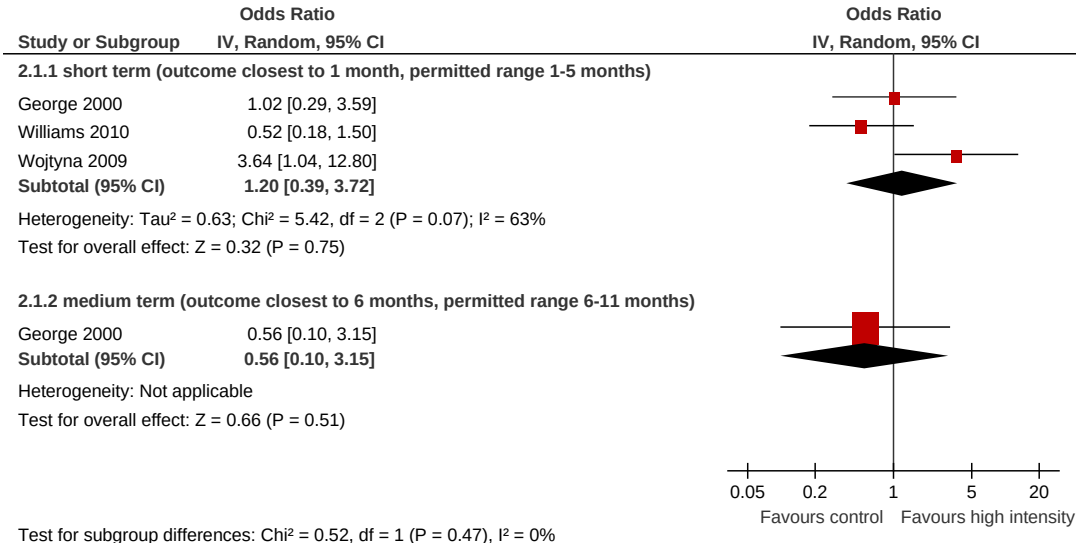
A random effects meta-analysis was conducted to assess the effect of high intensity behavioural therapy compared to control on point prevalence smoking cessation in PTSD. In a pooled analysis of two comparable studies in terms of package and delivery (**McFall 2005 [RCT, USA, +]; McFall 2010 [RCT, USA, ++]**), high intensity behavioural therapy significantly was effective for smoking cessation in the medium term (pooled OR 3.04, 95% CI 1.65-5.60, I^2=32%; Figure 2), and long term (OR 1.83, 95% CI 1.26-2.66; Figure 2) in PTSD. A similar significant effect was seen for continuous abstinence at long term follow-up (OR 2.26, 95% CI 1.30-3.91; **McFall 2010 [RCT, USA, ++]**).

Figure 2 **Meta-analysis of high intensity behavioural therapy for smoking cessation in PTSD**



A random effects meta-analysis was conducted to assess the effect of high intensity behavioural therapy compared to control on smoking cessation in schizophrenia. In a pooled analysis of three studies (**George 2000 [quasi-RCT, USA, +]; Wojtyna 2009 [NRCT, Poland -]; Williams 2010 [RCT, USA, +]**), high intensity behavioural therapy was no more effective for smoking cessation in the short term (pooled OR 1.20, 95% CI 0.39-3.72, I^2=63%; Figure 3), or in the medium term (OR 0.56, 95% CI 0.10-3.15; **George 2000 [quasi-RCT, USA, +]**; Figure 3) than control in schizophrenia. Please note for the **Williams 2010 (RCT, USA, +)** trial we have compared the effectiveness of high intensity versus medium intensity as defined empirically by the trial.

Figure 3 **Meta-analysis of high intensity behavioral therapy for smoking cessation in schizophrenia**



EVIDENCE STATEMENTS

ES1.1 There is moderate evidence from two trials (**McFall 2005 [RCT, USA, +]; McFall 2010 [RCT, USA, +]**) to suggest integrated tailored behavioural therapy was more effective for increasing smoking cessation in outpatients for PTSD in the short (pooled OR 3.04, 95% CI 1.65-5.60) and long (OR 1.83, 95% CI 1.26-2.66) term than usual standard of care (referral to a specialised smoking cessation clinic).

ES1.2 There is mixed weak evidence from four studies regarding the effectiveness of high intensity behavioural therapy in people with psychiatric disorders. One study (**Currie 2008 [Quasi-RCT, Canada, +]**) suggested high intensity behavioural therapy given for 8 weeks was marginally more effective than given for 4 weeks in outpatients; however no formal comparisons could be made to assess statistical significance. Evidence was mixed from two further studies where one study demonstrated no significant difference in abstinence between motivational interviewing or brief advice in 191 in-patients **(Brown 2003 [RCT, USA, +]**; long term outcome, OR 1.16, 95% CI 0.59-2.31), whereas the other demonstrated significantly fewer people smoked at short term follow-up in the high intensity behavioural therapy group compared to no intervention in 38 outpatients (**Kisely 2003 [NRCT, Australia, -])**. However, there was evidence from one study of 123 outpatients (**Morris 2011 [RCT, USA, +]**) which suggested high intensity behavioural therapy in addition to a quit-line service was more effective than quit-line service alone for reducing cigarette consumption (OR 3.16, 95% CI 1.04-9.65).

ES1.3 There is moderate evidence from three studies (**George 2000 [quasi-RCT, USA, +]; Wojtyna 2009 [NRCT, Poland, -]; Williams 2010 [RCT, USA, +]**) to suggest high intensity behavioural therapy is no more effective than lower intensity behavioural therapy for smoking cessation in the short (Pooled OR 1.20, 95% CI 0.39-3.72) or medium (OR 0.56, 95% CI 0.10-3.15) term in in-patients and outpatients with schizophrenia. Please note that two of these studies (**George 2000 [quasi-RCT, USA, +]; Williams 2010 [RCT, USA, +])** gave all participants NRT in addition to their behavioural therapy, and the intensity of the behavioural therapy in the control group of the **Williams 2010 [RCT, USA, +]** was relatively high.

The majority of evidence on high intensity behavioural therapy is directly applicable to the UK setting, as there is no reason to assume that the interventions could not be implemented in UK outpatient and in-patient settings. Six of the studies were conducted in the USA, with individual studies being conducted in Australia, Canada, China, and Poland.

Table 1 Summary evidence table for high intensity behavioural therapy

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Brown 2003 RCT, n=191	**Location:** USA **Setting:** In-patient	13-17 year olds, reporting smoking at least one cigarette per week for 4 weeks before hospitalisation, access to phone, DSM-IV criteria for anxiety disorder, disruptive and behavioural disorder, substance related disorder **Motivation:** Not reported	**Intervention:** Motivational interviewing, two 45 minute individual sessions while hospitalised. Following discharge received 2 NRT patch in those desired to quit, medically eligible, and smoked 10+ cigarettes per day. **Control:** Brief advice, 5-10 minutes of advice to quit smoking by study therapist. A copy of "I Quit!" self help pamphlet given too. NRT patch regimen allowed once after discharge **Outcome:** Point prevalence abstinence (7 day bio-verified by CO<10ppm and saliva cotinine <15ng/ml), number of cigarettes smoked per day, self-efficacy	+ **Limitations:** High participation refusal rate, caution needed to how generalisable the results are to general population of adolescent smokers, level of contact different between groups so difference may be due to this rather than content of treatment, specific to in-patients
Chen 2002 ITS, n=65	**Location:** China **Setting:** Outpatient	DSM – IV criteria for schizophrenia or schizoaffective disorder, 20+ cigarettes per day, participants who could stay for at least 60 minutes to participate in study, literate, willing to complete questionnaire **Motivation:** Not reported	**Intervention:** Smoking cessation programme – closed and time limited format. 8 sessions twice per week of 1 hour duration per session **Control:** No intervention **Outcome:** Point prevalence smoking abstinence (7 day)	- **Limitations: :** One psychiatric hospital, methods very unclear, no bio-verified smoking abstinence, control group had no intervention, short outcome
Currie 2008 Quasi-RCT, n=85	**Location:** Canada **Setting:** Outpatient	Severe and persistent mental illness (schizophrenia, mood disorders, other conditions), on one or more psychotic medications including antipsychotics, mood stabilizers, anxiolytics, antidepressants **Motivation:** Interest in quitting smoking	**Intervention:** 8 session version of smoking cessation program. NRT patches and gum encouraged **Control:** 4 session version of smoking cessation program. NRT patches and gum encouraged **Outcome:** Point prevalence abstinence (7 days, bio-verified with expired CO<10ppm), number of cigarettes per day in non-quitters	+ **Limitations:** Non-random assignment, different program lengths, low quit rate, lack of continuous abstinence

George 2000 Quasi-RCT, n=45	**Location:** USA **Setting:** Unclear	DSM-IV criteria for schizophrenia or schizoaffective disorder, and nicotine dependence, FTND≥5 **Motivation:** Motivated to quit smoking	**Intervention:** Specialised schizophrenia group therapy treatment, weekly group therapy for 10 weeks, comprising of 3 weeks of motivational enhancement therapy, and 7 weeks of psychoeducation, social skills training, relapse prevention strategies + NRT (21mg/day) **Control:** American Lung Association Programme, 7 weeks motivated behaviour group therapy programme and supportive group counselling during the remaining 3 weekly group sessions. Each session 60 minutes duration + NRT (21mg/day) **Outcome:** Point prevalence abstinence, continuous abstinence (weeks 8 to 12), expired CO levels	+ **Limitations:** Small sample size, not truly randomised with significant baseline differences, post-hoc analyses for atypical versus typical comparisons, setting unclear, no psychological outcomes assessed
Kisely 2003 UBA, n=38	**Location:** Australia **Setting:** Outpatient	10+ cigarettes smoked per day, 18-65 years of age, clinically stable, psychiatric diagnosis **Motivation:** Not reported	**Intervention:** 8 weekly 1.5 hour sessions behavioural therapy **Control:** No intervention **Outcome:** Retrieved case notes to assess the number of times tobacco use was recorded in the notes, FTND scores, urinary cotinine	- **Limitations:** High attrition rate, non-blinded assessment of outcome, no blinding of treatments, no control, short term follow-up, non-randomised design
Morris 2011 RCT, n=123	**Location:** USA **Setting:** Outpatient	Psychiatric diagnoses and continued to receive treatment as usual during the course of the study, at least 5 cigarettes per day, 18+ years of age, informed consent and participation in groups, English speaking **Motivation:** Interested in quitting regardless of motivational readiness to quit	**Intervention:** Quitline service and community tobacco cessation group, up to 10 sessions based on "Smoking Cessation for Persons with Schizophrenia" **Control:** Quitline service only, through fax referral **Outcome: :** Point prevalence abstinence (7 day, bio-verified by CO<6ppm), 50% reduction in self reported number of cigarettes smoked from baseline	+ **Limitations:** Small sample size, drop-out related to psychiatric diagnosis (highest in those with depression), training may have been insufficient for mental health illness population, no results reported for cessation for each treatment group, difference intensity of treatment for behavioural support which may be related to differences in outcome, rather than the content of the sessions

McFall 2005 RCT, n=66	**Location:** USA **Setting:** Outpatient	DSM-IV criteria for PTSD, 10+ cigarettes smoked per day **Motivation:** Willing to receive smoking cessation treatment	**Intervention:** Integrated care – 5 individual behaviour counselling cessations, once a week and one follow-up contact, duration about 20 minutes each **Control:** Usual standard of care – referred to Veterans Affairs Puget Sound Health Care Systems Smoking cessation clinic, one group orientation class, individual session in which receive treatment and behavioural counselling, received no tobacco-cessation interventions from PTSD clinic provider **Outcome:** Point prevalence abstinence (7 day, expired CO≤10ppm)	+ **Limitations:** No clearly demarcated quit date or end of intervention period, no biomarkers on long term smoking cessation, small sample size, different number of sessions between intervention and control, therefore differences may be due to number of contacts rather than content
McFall 2010 RCT, n=943	**Location:** USA **Setting:** Outpatient	DSM-IV diagnosis for PTSD, engaged in outpatient PTSD care, PTSD related to military service, 10+ cigarettes smoked per day on at least 15 out of 30 days before screening **Motivation:** Consented to receive cessation interventions	**Intervention:** Integrated care – PTSD clinicians delivered individual sessions based on 5 weekly core tobacco cessation sessions focusing on tobacco use education, behavioural skills for quitting smoking, setting a quit date and relapse prevention. Cessation medications allowed. Three follow-up monthly booster visits re-applied smoking cessation treatment to continued smokers **Control:** Usual standard of care - referral to specialised cessation clinics at each site, treatment within 6 weeks of referral, prescribed medications directly or through general practitioners **Outcome:** Prolonged abstinence (self-report and bio-verified by CO≤8ppm and urine cotinine<100ng/ml), point prevalence abstinence (7 day and 30 day)	++ **Limitations:** Selected sample of predominately older male Vietnam-era veterans with chronic PTSD and co-occurring depression, lack of blinding for outcome assessor, number of session differed between the groups, therefore difference could be related to higher contact rather than content of sessions
Williams 2010 RCT, n=100	**Location:** USA **Setting:** Outpatient	DSM-IV criteria for schizophrenia or schizoaffective disorder, more than 10 cigarettes smoked per day, atypical antipsychotic medication **Motivation:** Motivated to quit smoking	**Intervention:** Behavioural counselling – Treatment of Addiction to Nicotine in Schizophrenia (TANS) – high intensity treatment of 24 sessions (45 minutes duration each) + NRT patches (21mg/day) **Control:** Medication management (MM) – moderate intensity treatment of 9 sessions (20 minutes duration each) + NRT patches (21mg/day) **Outcome:** Continuous abstinence (bio-verified by	+ **Limitations:** Clinicians in trial were trained and delivered both TANS and MM treatments which could have blurred the distinction between the two treatments, NRT medication may have minimized the

			CO<10ppm), point prevalence abstinence (7 day), time to first lapse to smoking	behavioural therapy differences, different number of sessions, so difference may be due to number of contacts rather than content of sessions
Wojtna 2009 NRCT, n=44	**Location:** Poland **Setting:** In-patient	Mentally ill heavy smokers (diagnoses included schizophrenia and depression) **Motivation:** Not reported	**Intervention:** CBT, 12 weekly 2 hour therapeutic sessions concentrating on enhancing self-esteem, and 12 weekly educational sessions **Control:** Education training sessions only **Outcome:** Smoking abstinence, self-reported number of cigarettes smoked per day	- **Limitations: :** Lack of randomisation, lack of blinding, no intention to treat analysis, lack of information about population and methods

LOW INTENSITY BEHAVIOURAL THERAPY INTERVENTIONS

Axtmayer 2011 (RCT, USA, -) A randomised controlled pilot trial was conducted to assess the effectiveness of a telephone care coordination programme in 128 outpatients who were referred by their mental health providers. Participants were randomised to receive telephone counselling from a State Quitline, or face-to-face counselling from a specialist stop smoking advisor.

SMOKING CESSATION OUTCOMES

The study reported a significant reduction in the number of cigarettes smoked from baseline to follow-up at 2 months for participants who received at least one counselling session in both the State Quitline (mean 16.1 versus 9.3 cigarettes/day; p<0.0009) and Veteran Affairs counsellor (mean 17.9 versus 11.1 cigarettes/day; p=0.001) groups. No comparisons were made between treatment groups.

Dixon 2009 (cluster RCT, USA, ++) A cluster RCT was conducted to assess the effectiveness of a low intensity behavioural intervention in 304 outpatients with schizophrenia or schizoaffective disorders from mental health clinics. The low intensity behavioural intervention was implemented either immediately in 3 mental health clinics, or delayed for 6 months in 3 other mental health clinics. The intervention consisted of the '5 A's', based on i) assessing whether the participant smoked, ii) advising identified smokers to quit immediately, iii) assess the willingness of the participant to make a quit attempt within the next 30 days, iv) assist those identified as willing to make optimal quitting plans, which included provision of education handouts, v) arrange for next visit, which was likely to include group behavioural therapy.

SMOKING CESSATION OUTCOMES

The study demonstrated no significant difference from baseline to 6 months follow-up for whether the participant had smoked in the last 7 days between the immediate and delayed implementation groups (self-report smoking status, p=0.73; expired CO<10ppm, p=0.14). Additionally, no significant difference was seen from baseline to 6 months follow-up for in the number of cigarettes smoked in the last 7 days between the immediate and delayed implementation groups (p=0.36).

EVIDENCE STATEMENTS

ES2.1 There is very weak evidence from one RCT in 128 mental health outpatients (**Axtmayer 2011 [RCT, USA, -]**) to suggest brief intervention either from using a Quitline or a face-to-face counsellor resulted in a significant reduction in the number of cigarettes smoked per day from baseline (Mean reductions from 16.1 to 9.3 cigarettes/day, 17.9 to 11.1 cigarettes/day, respectively).

ES2.2 There is moderate evidence from one cluster RCT in 304 outpatients with schizophrenia or schizoaffective disorders (**Dixon 2009 [cluster RCT, USA, ++]**) to suggest low intensity behavioural support resulted in no significant difference in abstinence or smoking consumption.

The evidence from the two studies based on low intensity behavioural therapy is directly applicable to the UK setting as there is no reason to assume the interventions could not be implemented in UK outpatient and in-patient settings. Both studies were conducted in the USA.

Table 2 Summary evidence table for low intensity behavioural therapy

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Axtmayer 2011 RCT, n=128	**Location:** USA **Setting:** Outpatient	Smokers with mental illness **Motivation:** not reported	**Intervention:** Telephone care coordination programme with counselling from a State Quitline **Control:** Face-to-face counselling from a Veterans Affairs counsellor Outcome: Number of cigarettes smoked per day	- **Reasons:** Insufficient details given in abstract, small sample size, criteria for mental health disorder not provided, only performed within group comparisons, no bio-verification of smoking status
Dixon 2009 Cluster RCT, n=304	**Location:** USA **Setting:** Outpatient	DSM-IV criteria for schizophrenia spectrum disorder or affective psychoses or other psychoses, 18-64 years, at least 1 cigarette per month, English speaking, at least 2 appointments with psychiatrist in past 6 months, informed consent **Motivation:** Not reported	**Intervention:** Clinics wide immediate implementation of the 5 A's (i. assessing whether the participant smoked, ii. advising identified smokers to quit immediately, iii. assess the willingness of the participant to make a quit attempt within the next 30 days, iv. assist those identified as willing to make optimal quitting plans, which included provision of education handouts, v. arrange for next visit, which was likely to include group behavioural therapy) **Control:** Delayed implementation of 5 A's for 6 months, then implemented after delay **Outcome:** Point prevalence (7 day, bio-verified by expired CO<10ppm), self-report number of cigarettes smoked per week	++ **Limitations:** Relatively short term follow-up, participants not selected based on motivation, sites may have varied

CONTINGENCY PAYMENTS

CONTINGENCY PAYMENTS

Roll 1998 (USA, -) A non-randomised within-subject reversal design (Active →Control→Active) was conducted to assess the effectiveness of contingency payments in 11 outpatients undergoing treatment for schizophrenia or schizoaffective disorders, of which none considered ceasing their smoking upon entering the trial. During the baseline phases at weeks 1 and 3, participants were visited once per day in the afternoon and given $5 US for their participation. During the treatment phase in week 2, participants were visited three times per day and received cash payments if they were deemed abstinent as assessed by expired CO levels≤11ppm. $3 US was given for the first reading below the cut-off, and $0.50 for each subsequent reading throughout the week. Participants also received $10 US bonuses whenever three consecutive reading were below the cut-off in addition to their scheduled payments. Thus the total amount that could be received across all three conditions was $147 US.

SMOKING CESSATION OUTCOMES

There was a significant difference in the mean expired CO levels across the three conditions (mean 35.9 versus 15.9 versus 25.9ppm; $p<0.05$). Additionally, the total numbers of expired CO levels≤11pppm between the baseline phases and the active phase were significantly different (baseline 1 versus active, p=<0.05; baseline 2 versus active, $p<0.05$); however, no significant difference was seen between the baseline phases ($p>0.05$).

EVIDENCE STATEMENT

ES3.1 Weak evidence from one non-randomised within-subject reversal design trial (**Roll 1998 [NRCT, USA, -]**) suggested contingency payments rewards significantly reduced expired CO levels in 11 outpatients undergoing treatment for schizophrenia or schizoaffective disorders.

The evidence for contingency payments as an intervention for smoking cessation is potentially applicable to the UK as intervention may be feasible to the UK setting; however, this does not reflect current clinical practice in the UK. The study was conducted in the USA.

Table 3 Summary evidence table for contingency payments

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Roll 1998 Within participant reversal design, n=11	**Location:** USA **Setting:** Outpatient	DSM –IV schizophrenia or schizoaffective disorder, undergoing treatment for schizophrenia, current cigarette smokers, 18+ years of age, expired CO≥18ppm **Motivation:** None considering quitting cigarette smoking up on entering the study	**Intervention:** Contingency payment, week 2 of trial, visited three times per day, if expired CO was ≤11pm, they received payment. Total amount if abstinent on all 15 reading for the week was $147 US **Control:** Week 1 and 3, visited once per day, received $5 US for each day irrespective of CO reading **Outcome:** Number of expired CO readings≤11ppm, mean expired CO levels	- **Limitations:** More visits in the intervention phase than control phase, small sample size, abstinence not assessed, short follow-up

PHARMACOTHERAPIES

BUPROPION

Hertzberg 2001 (RCT, USA, +) A RCT was conducted to assess the effectiveness of bupropion in 15 male combat veterans outpatients who had a primary diagnosis of PTSD. Participants were randomised to bupropion SR (initial dose 150mg every morning for 3-4 days, increasing to 150mg given twice daily) or a matching placebo, for 12 weeks. The target quit date was set for at least one week post commencement of treatment. The study assessed outcomes at week 2, week 8, week 12 and 6 months. Sustained abstinence bio-verified by expired CO was measured, however no formal analyses were conducted due to 80% (4 out of 5 participants) of the placebo group failing to stop smoking or sustain their cessation and through not completing the 12 week trial.

SMOKING CESSATION OUTCOMES

At 12 weeks follow-up, no significant difference in sustained abstinence was seen between the groups (6/10 versus 1/5; p=0.282).

Weinberger 2008 (RCT, USA, -) A randomised controlled pilot trial was conducted to assess the effectiveness of bupropion for smoking cessation in 5 outpatients with a diagnosis of bipolar. Participants were randomised to receive bupropion intermediate release formulation (75mg once/day for 3 days increasing to 150mg [SR formulation] orally once/day for 4 days, increasing to 150mg orally twice/day by day 15), or a placebo, for a total of 10 weeks. All of the participants received weekly manualised behavioural group therapy session.

SMOKING CESSATION OUTCOMES

One out of the 2 patients randomised to bupropion achieved self-reported smoking abstinence with bio-verification using expired CO compared to none of the 3 participants in the placebo group.

Akbarpour 2010 (RCT, Iran, +) A RCT was conducted to assess the effectiveness of bupropion in 32 male in-patients diagnosed with schizophrenia. Participants were randomised to bupropion SR (150mg/day orally for 3 days, increasing to 300mg/day orally), or placebo, for 8 weeks.

SMOKING CESSATION OUTCOMES

The study demonstrated a significant reduction in the number of cigarettes smoked per day from baseline to week 8 in the bupropion group (mean 15.0 versus 11.1; p=0.008), but no significant reduction in the placebo group (mean 13.1 versus 13.4; p=0.72). A multivariable analysis demonstrated bupropion was significantly associated with increased likelihood of smoking abstinence at 12 weeks compared to placebo (p=0.03, data were not presented in a useable format for meta-analysis).

Bloch 2010 (RCT, Israel, -) A RCT was conducted to assess the effectiveness of bupropion in 61 outpatients with diagnoses of schizophrenia or schizoaffective disorders, who expressed a strong desire to quit or at least significantly reduce the number of cigarettes smoked. Participants received either bupropion at an initial dose of 150mg/day for 3 days increasing to 150mg twice per day, or placebo, for 14 weeks following a 2 week medication stabilisation period. All participants received 15 sessions of CBT over a 14 week period.

SMOKING CESSATION OUTCOMES

The study reported no significant treatment effect was seen for the self-reported number of cigarettes smoked per day between the bupropion and placebo groups at the end of 14 weeks ($p>0.1$); however, a significant reduction in the number of cigarettes smoked was seen when comparing baseline to week 14 ($p<0.001$).

Evins 2001 (RCT, USA, +) A RCT was conducted which assessed the effectiveness of bupropion in 18 outpatients diagnosed with schizophrenia, who had a desire to quit smoking. All participants received brief advice about smoking cessation, and were then randomised to bupropion SR (150mg/day), or placebo, for 12 weeks. Participants received CBT group therapy (9 weekly sessions, 1 hour duration each).

SMOKING CESSATION OUTCOMES

The study demonstrated no significant difference in abstinence from smoking (bio-verified by expired CO levels or serum cotinine) between the bupropion and placebo groups on the target quit date (3/9 versus 1/9; $p=0.58$), and at week 12 (sustained abstinence, 1/9 versus 0/9). However, at week 12, some evidence of a significant difference was seen between the treatment groups for those who achieved at least a 50% reduction in the number of self-reported cigarettes smoked per day (bio-verified with 30% reduction in expired CO levels) (6/9 versus 1/9; $p=0.05$); but no significant effect was seen between the treatment groups at the 6 month follow-up (3/9 versus 1/9). Levels of expired CO were significantly more reduced from baseline in the bupropion group as compared to placebo at week 12 (mean difference, 14.8ppm; $p<0.01$) and week 24 (mean difference, 14.3ppm; $p=0.03$). Additionally, the change in serum cotinine levels from baseline to week 12 were lower in the bupropion group compared to placebo (mean difference, 108ng/ml).

Evins 2005 (RCT, USA, ++) A RCT was conducted to assess the effectiveness of bupropion in 57 outpatients diagnosed with schizophrenia or schizoaffective disorders, who were willing to set a smoking quit date. Participants were randomised to bupropion (150mg/day for 7 days, if tolerated medication okay, then dose was increased to 150mg twice/day for 11 weeks), or placebo, for 12 weeks. All participants received 12 weekly sessions of CBT.

SMOKING CESSATION OUTCOMES

The study demonstrated those taking bupropion were significantly more likely to achieve continuous abstinence compared to placebo at 1 week immediately following target quit date, where 7 day point prevalence abstinence (bio-verified by CO<9ppm) was 36% versus 7%, respectively ($p=0.016$).

The significant difference in 7 day point prevalence abstinence was maintained to week 12 (16% versus 0%; p=0.043); however, no significant difference between the treatment groups was seen at week 14 (8% versus 3.6%) or at week 24 (4.0% versus 3.6%). From weeks 4-12, expired CO levels were significantly lower in the bupropion group compared to placebo (p=0.029), with mean reductions in expired CO levels significantly different from baseline to week 12 (mean reduction, 44% versus 20%), but not significant difference was seen in mean reductions of expired CO levels for weeks 14 to 24. Mean duration of abstinence was significantly longer in the bupropion group compared to placebo (mean, 2.0 versus 0.25 weeks; p=0.005). The change from baseline in the self-reported number of cigarettes smoked per day between the bupropion and placebo groups was significantly different at week 12 (mean reduction, 26.5 versus 10.2 cigarettes/day; p=0.002), and week 14 (p=0.018); but the difference was not statistically significant at week 18 or week 24.

Evins 2007 (RCT, USA, ++) A RCT was conducted which assessed the effectiveness of bupropion in 51 outpatients diagnosed with schizophrenia, who were willing to set a smoking quit date. Participants were randomised to receive bupropion (150mg per day for 7 days, increasing to twice daily for 11 weeks), or placebo (using the regimen as the active group), for 12 weeks. All participants additionally received 12 one hour weekly smoking cessation programme sessions. Following setting a target quit date; all participants received NRT patches (21mg/day for 4 weeks, decreasing to 14mg/day for 2 weeks, decreasing to 7mg/2 weeks). NRT gum (2mg) was used as needed up to a maximum dose of 18mg/day.

SMOKING CESSATION OUTCOMES

The study demonstrated 4 week abstinence (week 4-8) was significantly more likely in the bupropion group compared to the placebo group (52% versus 19%; OR 4.6, 95% CI 1.3-16; p=0.014); however, differences between the groups after week 8 became non-significant (week 12 [bio-verified by CO], OR 2.4, 95% CI 0.66-8.4; 3 months follow-up, OR 3.0, 95% CI 0.92-7; 12 month follow-up, OR 1.6, 95% CI 0.25-11). Significant differences were seen in the proportion of participants achieving at least a 50% reduction in smoking (week 12, 60% versus 31%, OR 3.4, 95% CI 1.1-10, p=0.036; week 24, 32% versus 7.7%, OR 5.7, 95% CI 1.1-30, p=0.039); however no significant difference was seen between the groups at short term follow-up (8 weeks, 60% versus 35%, OR 2.8, 95% CI 0.91-8.8). The study also reported differences in the number of cigarettes smoked per day between the bupropion and placebo groups at week 12 (mean difference, -21 versus -11 cigarettes/day) and at week 24 (mean difference, -9.5 versus -2.9 cigarettes/day); however no significance levels were reported. Expired CO levels were significantly lower in the bupropion group compared to placebo from weeks 4-24 (mean difference, -7.6ppm; p=0.006), and at each time point (p=0.002).

Fatemi 2005 (RCT, USA, -) A randomised controlled cross-over trial was conducted to assess the effectiveness of bupropion for smoking reduction in 10 outpatients with a diagnosis of schizophrenia or schizoaffective disorders, who were encouraged to reduce their smoking consumption rather than cease smoking entirely. Participants were randomised to bupropion (dose not stated), or placebo, in a cross-over design with a one week washout period between treatments.

The treatment phases were given for three weeks and outcome measures were taken at the end of the third week.

SMOKING CESSATION OUTCOMES

The study reported no difference in the self-reported number of cigarettes smoked per day between the bupropion and placebo groups; however, there appeared to be reductions from baseline to week 3 in expired CO levels, urine cotinine and metabolite levels during the bupropion phase, whereas these measures all increased during the placebo phase from baseline to week 3.

George 2002 (RCT, USA, ++) A RCT was conducted to assess the effectiveness of bupropion in 32 outpatients with schizophrenia or schizoaffective disorders who expressed a strong desire to quit smoking. Participants were randomised to bupropion SR (initial dose 150mg orally daily for 3 days increasing to 150mg orally twice per day), or matching placebo, for 10 weeks. All participants additionally received smoking cessation group therapy for 10 weeks on a weekly basis with each session lasting 60 minutes. The target quit date was during the 3rd group therapy session on week 3.

SMOKING CESSATION OUTCOMES

At 10 weeks follow-up, the study demonstrated bupropion was significantly more likely to result in continuous abstinence (week 7-10, bio-verified by CO<10ppm) compared to placebo (37.5% versus 6.3%; p<0.05). However at 6 month follow-up, no significant difference was seen in the 7 day point prevalence estimates between the bupropion and placebo groups (18.8% versus 6.3%; p=0.29). Bupropion significantly reduced CO levels compared with placebo (p<0.05), and a significant reduction in the self-reported number of cigarettes smoked per day in the bupropion groups as compared to placebo (p<0.05).

Li 2009 (RCT, China, -) A RCT was conducted to assess the effectiveness of bupropion in 69 male in-patients who were diagnosed with schizophrenia. Participants received bupropion (75mg twice/day for 1 week, increasing to 150mg twice/day for 3 weeks), or placebo, for 4 weeks.

SMOKING CESSATION OUTCOMES

The study reported a significant decrease in the number of cigarettes used per day between the bupropion and placebo groups at the end of the first week of treatment (p<0.01), at the end of week 4 (p<0.01), and at the end of the trial (week 8, p<0.01).

Weiner 2011b (RCT, USA, ++) A RCT was conducted to assess the effectiveness of bupropion in 46 outpatients diagnosed with schizophrenia or schizoaffective disorders, who were interested in quitting or cutting down their smoking. Participants were randomised to receive bupropion SR (150mg/day for 3 days, increasing to 150mg twice/day), or placebo, for 12 weeks. The randomised treatments started on week 2. Participants additionally received 9 week support group smoking programme, with NRT being offered to all, from baseline (week 0).

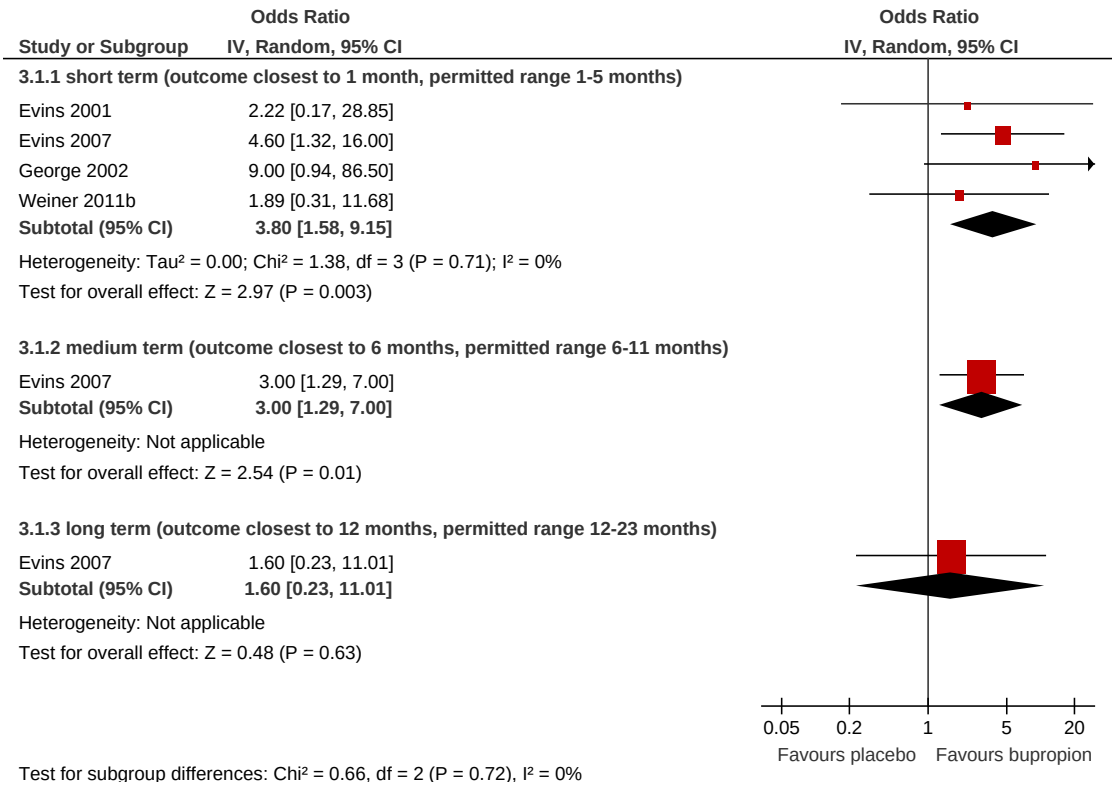
SMOKING CESSATION OUTCOMES

The study demonstrated no significant difference in sustained abstinence (week 10-14, bio-verified by CO<10ppm) between the bupropion and placebo groups (18% versus 11%; p=0.67). Weekly point prevalence abstinence numerically favoured the bupropion group over the course of the trial; however, no statistically significant difference was detected (p=0.29). Additionally, no significant differences were seen between the treatment groups over the course of the trial for expired CO levels (p=0.54), FTND scores (p=0.16), or urinary cotinine levels (p=0.13).

META-ANALYSIS FOR BUPROPION

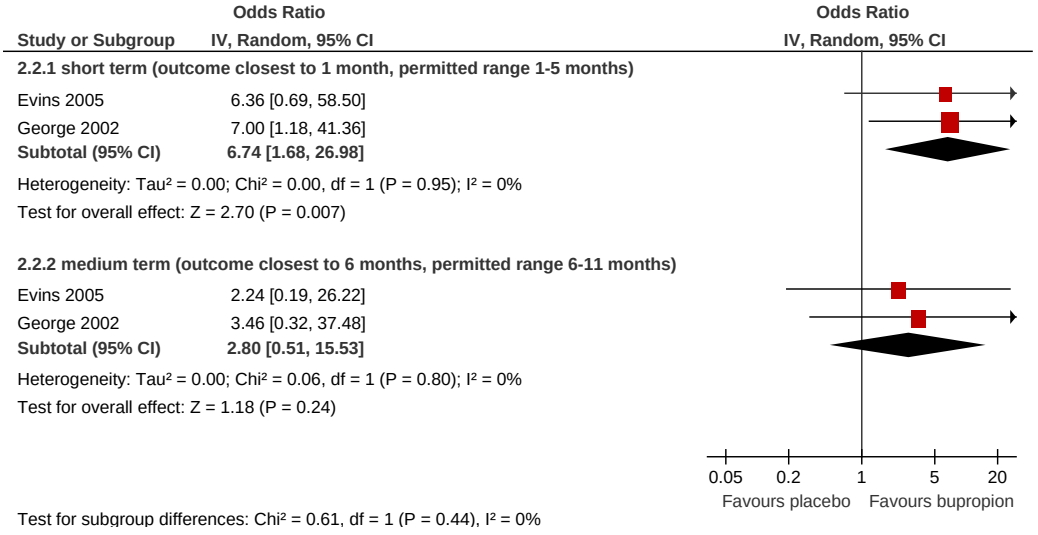
A random effects meta-analysis was conducted to assess the pooled effectiveness of bupropion as compared to placebo on **continuous abstinence** at short, medium and long term outcomes in schizophrenia or schizoaffective disorders. A pooled analysis of 4 studies demonstrated bupropion was effective for short term smoking cessation (OR 3.80, 95% CI 1.58-9.15, I^2=0%; Figure 4). Findings from one study suggested bupropion was effective at medium term (OR 3.00, 95% CI 1.29-7; Figure 4); however, there was no evidence that it was effective at long term (OR 1.60, 95% CI 0.23-11.01; Figure 4). Please note that all the participants in two of the trials in the meta-analysis received NRT (**Evins 2007 [RCT, USA, ++]; Weiner 2011b [RCT, USA, ++]**).

Figure 4 **Meta-analysis of bupropion for smoking cessation (continuous abstinence) in schizophrenia**



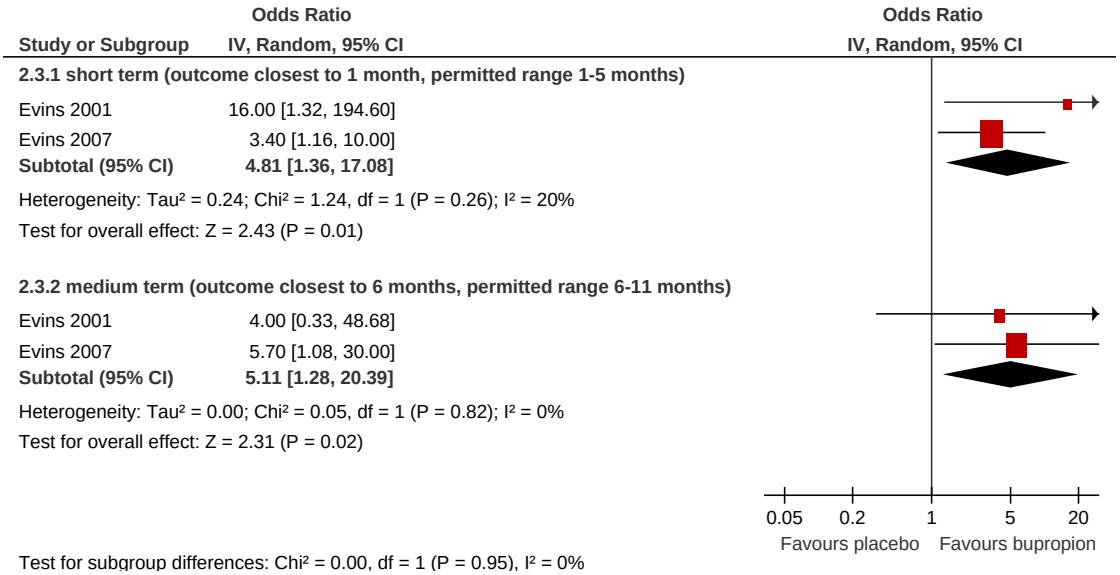
A random effects meta-analysis was conducted to assess the pooled effectiveness of bupropion as compared to placebo on **7 day point prevalence** abstinence at short and medium outcomes in schizophrenia or schizoaffective disorders. A pooled analysis of 2 studies demonstrated bupropion was effective for short term smoking cessation (OR 6.74, 95% CI 1.68-26.98, I^2=0%; Figure 5), but not at medium term outcome (OR 2.80, 95% CI 0.51-15.53, I^2=0%; Figure 5).

Figure 5 **Meta-analysis of bupropion for smoking cessation (point prevalence abstinence) in schizophrenia**



A random effects meta-analysis was conducted to assess the pooled effectiveness of bupropion as compared to placebo on **smoking reduction** of at least 50% in the number of cigarettes smoked per day (bio-verified by at least 30% or 40% reduction in expired CO levels) at short and medium outcomes in schizophrenia or schizoaffective disorders. A pooled analysis of 2 studies demonstrated bupropion was effective for short term smoking reduction (OR 4.81, 95% CI 1.36-17.08, I^2=20%; Figure 6) and at medium term (OR 5.11, 95% CI 1.28-20.39, I^2=0%; Figure 6). Please note that all of the participants received NRT in one of the trials included in the meta-analysis (**Evins 2007 [RCT, USA, ++]**).

Figure 6 **Meta-analysis of bupropion for 50% reduction in smoking in schizophrenia**



EVIDENCE STATEMENTS

ES4.1 There is weak evidence from one trial (**Hertzberg 2001 [RCT, USA, +]**) to suggest bupropion (300mg/day) is not effective for smoking cessation at short term follow-up in 15 male outpatients with PTSD.

ES4.2 There is very weak evidence from one trial (**Weinberger 2008 [RCT, USA, -]**) to suggest bupropion (300mg/day) is not effective for smoking cessation at short term follow-up in 5 outpatients with bipolar disorder.

ES4.3 There is strong evidence from pooled analyses comprising a total of five trials (**George 2002 [RCT, USA, ++]; Weiner 2011b [RCT, USA, ++]; Evins 2007 [RCT, USA, ++]; Evins 2001 [RCT, USA, +]; Evins 2005 [RCT, USA, ++]**) that bupropion (300mg/day) is effective for increasing smoking cessation in the short term in outpatients with schizophrenia (Pooled OR 3.80, 95% CI 1.58-9.15); but mixed strong evidence from pooled analyses comprising a total of three trials (**Evins 2007 [RCT, USA, ++]; George 2002 [RCT, USA, ++]; Evins 2005 [RCT, USA, ++]**) regarding the effectiveness of bupropion (300mg/day) for smoking cessation in the medium term in outpatients with schizophrenia (continuous abstinence, OR 3.00, 95% CI 1.29-7.00; point prevalence abstinence, pooled OR 2.80, 95% CI 0.51-15.53). Also, there is moderate evidence from one trial (**Evins 2007 [RCT, USA, ++]**) that bupropion is not effective for smoking cessation in the long term in outpatients with schizophrenia (OR 1.60, 95% CI 0.23-11.01).

ES4.4 There is moderate evidence from pooled analysis of two trials (**Evins 2007 [RCT, USA, ++]; Evins 2001 [RCT, USA, +]**) that bupropion (300mg/day) is effective for smoking reduction in the short term (Pooled OR 4.81, 95% CI 1.36-17.08) and medium (Pooled OR 5.11, 95% CI 1.28-20.39) term in outpatients with schizophrenia; however, there is very weak evidence from one trial (**Fatemi 2005 [RCT, USA, -]**) to suggest bupropion (dose not stated) had no significant effect on smoking reduction assessed as number of cigarettes per day smoked in outpatients with schizophrenia.

The evidence from the studies based on bupropion is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. The majority of studies were conducted in the USA, with individual studies being conducted in China, Iran, and Israel.

Table 4 Summary evidence table for bupropion

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Akbarpour, 2010 RCT, n=32	**Location:** Iran **Setting:** In-patients	Male smoking with schizophrenia (DSM-IV-TR) **Motivation:** not reported	**Intervention:** Bupropion SR (300mg/day) **Control:** Placebo **Outcome:** Self-reported smoking cessation	+ **Limitations:** Unclear methods used for randomization, unclear ITT analysis, small sample size, short follow-up, no bio-verification of abstinence
Bloch 2010 RCT, n=61	**Location:** Israel **Setting:** Outpatient	DSM-IV-TR criteria for schizophrenia or schizoaffective disorder, clinically stable, stable dose or anti-psychotic drug at least one month prior to start date, stable cigarette habits **Motivation:** Expressed strong desire to quit or at least significantly reduce the number of cigarettes smoked	**Intervention:** Following 2 week stabilisation period, Bupropion SR (300mg/day) and CBT **Control:** Placebo and CBT **Outcome:** Self-reported cigarette consumption	- **Limitations:** Small sample size, self-report outcome, completers analysis when high drop-out rate, short follow-up
Evins 2001 RCT, n=18	**Location:** USA **Setting:** Outpatient	DSM-IV diagnosis of schizophrenia, stable dose of antipsychotic medication for at least 4 weeks, reported cigarette use greater than half a packet per day **Motivation:** Desire to quit smoking	**Intervention:** Bupropion SR (150mg/day) + CBT **Control:** Placebo + CBT **Outcome:** Point prevalence abstinence (bio-verified by CO<9ppm or serum cotinine<14ng/ml), 50% reduction from baseline in self-reported cigarettes smoked per day (bio-verified by at least 30% reduction in expired CO), expired CO levels	+ **Limitations:** Small sample size, insufficient information regarding population
Evins 2005 RCT, n=57	**Location:** USA **Setting:** Outpatient	DSM-IV criteria for schizophrenia or schizoaffective disorder, depressed type, stable symptoms and a stable dose of	**Intervention:** Bupropion SR (300mg/day) + CBT **Control:** Placebo + CBT **Outcome:** Point prevalence and continuous abstinence from smoking in past 7 days (bio-verified by CO<9ppm), self-reported number of cigarettes smoked in past 7 days ,	++ **Limitations:** Intention to treat analysis not used

		antipsychotic medication for 30 days, baseline Hamilton Depression score<20, smoked 10+ cigarettes per day **Motivation:** Willing to set a quit date within 4 weeks of enrolment	expired CO levels, duration of abstinence	
Evins 2007 RCT, n=51	**Location:** USA **Setting:** Unclear	Adults with schizophrenia DSM-IV, capacity to consent, stable psychiatric symptoms and antipsychotic dose for 30 days or more, smoked 10+ cigarettes per day for past year **Motivation:** Willing to set a smoking quit date within 4 weeks of enrolment	**Intervention:** Bupropion SR (300mg/day) + behavioural support + NRT patches (21mg/day) + NRT gum (as needed) **Control:** Placebo + behavioural support + NRT patches (21mg/day) + NRT gum (as needed) **Outcome:** Smoking cessation at 3 months, continuous abstinence (bio-verified by CO, cut off not reported), 50% reduction in smoking compared to baseline by self-report (bio-verified by at least 40% reduction in expired CO levels), number of cigarettes smoked per day, expired CO levels	++ **Limitations:** Small sample size, insufficient information regarding source population and setting
Fatemi 2005 RCT, n=10	**Location:** USA **Setting:** Outpatient	DSM-IV criteria for schizophrenia or schizoaffective disorder and nicotine dependence. **Motivation:** Encouraged to reduce smoking rates rather than quit entirely	**Intervention:** Bupropion HCL (dose not stated) **Control:** Placebo **Outcome:** Self-reported number of cigarettes smoked per day, expired CO levels, urine cotinine levels	- **Limitations:** Small sample size, short intervals between outcome timings, outcomes measured at several time points, but only selected ones reported in paper, no statistical results presented, insufficient details regarding dose of treatment
George 2002 RCT, n=32	**Location:** USA **Setting:** Outpatient	DSM-IV criteria for schizophrenia or schizoaffective disorders with nicotine dependence, FTND≥5, CO≥10ppm, plasma cotinine≥150ng/ml, clinically stable on psychotic and affective symptomatology **Motivation:** Expressed a strong	**Intervention:** Bupropion (300mg/day) + smoking cessation group therapy **Control:** Placebo + smoking cessation group therapy **Outcome:** Point prevalence abstinence (7 day, bio-verified by CO<10ppm), continuous abstinence (weeks 7 to 10, bio-verified by CO<10ppm), CO levels, number of cigarettes smoked per day	++ **Limitations:** Small sample size, lack of objective assessment of compliance with study medications

		desire to quit smoking		
Hertzberg 2001 RCT, n=15	**Location:** USA **Setting:** Outpatient	DSM-IV for primary diagnosis of PTSD, no psychotropic medication or stable psychotic regimen, same dose and drug for 6 months **Motivation:** Not reported	**Intervention:** Bupropion (300mg/day) **Control:** Placebo **Outcome:** Sustained abstinence	+ **Limitations:** Small sample size, limited outcomes, funded by pharmaceutical company
Li 2009 RCT, n=69	**Location:** China **Setting:** In-patient	Male participants with schizophrenia, but criteria for diagnosis not reported **Motivation:** Not reported	**Intervention:** Bupropion (300mg/day) **Control:** Placebo **Outcome:** Self-reported number of cigarettes smoked per day	- **Limitations:** Short follow up, insufficient methodological details, lack of bio-verified smoking status
Weinberger 2008 RCT, n=5	**Location:** USA **Setting:** Outpatient	DSM-IV diagnosis of bipolar disorder and nicotine dependent cigarette smokers, 10+ cigarettes per day, expired CO>10ppm, clinically stable **Motivation:** Not reported	**Intervention:** Bupropion SR (300mg/day) **Control:** Placebo **Outcome:** Smoking abstinence (bio-verified with expired CO<10ppm)	- **Limitations:** Eligible subjects difficult to recruit, very small sample size, high drop-out rate
Weiner 2011b RCT, n=46	**Location:** USA **Setting:** Outpatient	DSM-IV diagnosis schizophrenia or schizoaffective disorder, clinically stable, ≥10 cigarettes per day **Motivation:** Interested in quitting or cutting down	**Intervention:** Bupropion (300mg/day) **Control:** Placebo **Outcome:** Sustained abstinence (weeks 10-14, bio-verified by CO<10ppm), point prevalence abstinence, expired CO levels, urine cotinine levels, FTND	++ **Limitations:** Small sample size, short follow-up

CLOZAPINE

Clozapine is an atypical antipsychotic medication. Switching from typical antipsychotic medications to atypical antipsychotic medications has been suggested to reduce smoking.

McEvoy 1995 (RCT, USA, -) A randomised controlled three-arm pilot trial was conducted to assess the effectiveness of the atypical antipsychotic clozapine for smoking cessation in 12 chronically hospitalised in-patients diagnosed with chronic schizophrenia. All participants initially received haloperidol (typical antipsychotic) (20mg/day) for 2 weeks; then participants were randomised to clozapine either at a low plasma level range (50-150ng/ml), medium plasma level range (200-300ng/ml), or high plasma level range (350-450ng/ml), for 12 weeks. Participants were normally only allowed to smoke one cigarette per hour on the wards of the hospital; however, during the trial they were allowed free access to cigarettes over a 120 minute period in the afternoon when outcome measures were collected.

SMOKING CESSATION OUTCOMES

The study demonstrated significant reductions in the change from baseline to week 12 in number of cigarettes smoked per 120 minute period (p=0.02), and significant reductions in the levels of expired CO at 12 weeks (p=0.04); however, only the medium range group was associated with a significantly greater decline in expired CO than compared to the low range group.

McEvoy 1999 (RCT, USA, +) A randomised controlled three-arm trial was conducted to assess the effectiveness of clozapine in 55 smoking and 15 non-smoking in-patients with schizophrenia who had previously failed to respond to adequate treatment regimens of at least two atypical antipsychotic medications. Participants were initially measured at baseline for 1-2 weeks whilst they received haloperidol or fluphenazine (typical antipsychotics, mean dose 21mg/day, range 5-60mg/day) and an anti-cholinergic, anti-Parkinson's disease drug. Following baseline measurements, participants were randomised to receive clozapine either at a low plasma level range (50-150ng/ml), medium plasma level range (200-300ng/ml), or high plasma level range (350-450ng/ml), for 12 weeks. Participants were normally only allowed to smoke one cigarette per hour on the wards of the hospital; however, during the trial they were allowed free access to cigarettes over a 120 minute period in the afternoon when outcome measures were collected.

SMOKING CESSATION OUTCOMES

In the 55 smokers, participants receiving higher plasma level doses (combination of medium and high plasma level groups) were significantly more likely to have a greater reduction in the number of cigarettes smoked during the 120 minutes between baseline and 12 weeks compared to the low plasma level group (p=0.005). However, no significant differences were seen between the higher plasma level groups compared to the low plasma level group in the change from baseline to week 12 for expired CO levels (p=0.24), plasma nicotine levels (p=0.57), or plasma cotinine levels (p=0.27).

De Leon 2005 (RCT, USA, +) A RCT was conducted to assess the effectiveness of clozapine in 50 smoking and non-smoking in-patients with moderate severity of schizophrenia or schizoaffective disorders, which had not shown a satisfactory clinical response to at least 3 neuroleptic drugs. Participants initially receive haloperidol (10mg/day) for 4 weeks; and then were randomised to receive clozapine either at 100mg/day, 300mg/day or 600mg/day doses, for 16 weeks. Participants who were non-responsive were included in a second and/or third 16 week double blind trial where they received the remaining doses. For the 38 current smokers, cigarettes were provided free of charge to the participants at standard smoking time in the unit.

SMOKING CESSATION OUTCOMES

The study demonstrated no significant changes in plasma nicotine from baseline to week 16 in the 100mg/day (p=0.7), 300mg/day (p=0.4), 600mg/day (p=0.6) treatment groups.

EVIDENCE STATEMENT

Clozapine is an atypical (new generation) antipsychotic medication. There is emerging evidence that switching from typical antipsychotic medications to atypical antipsychotic medications reduces smoking.

ES5.1 There is moderate evidence from three trials (**McEvoy 1995 [RCT, USA, -]; McEvoy 1999 [RCT, USA, +]; De Leon 2005 [RCT, USA, +]**) suggesting higher doses of clozapine (350-600mg/day) in in-patients with schizophrenia or schizoaffective disorders may reduce the self-reported number of cigarettes smoked per day; however, no effects were seen on objective markers of smoking consumption (expired CO or plasma nicotine levels).

The evidence from the three studies based on clozapine as a smoking cessation medication is potentially applicable to the UK setting as there is no reason to assume that the intervention would not have the same outcome in a UK setting. All three studies were conducted in the USA.

Table 5 Summary evidence table for clozapine

Study details	Location and setting	Description of population	Outline of study	Internal validity score
De Leon 2005 RCT, n=50	**Location:** USA **Setting:** In-patient	DSM-III-R schizophrenia or schizoaffective disorder, not shown satisfactory clinical response to treatment with at least three neuroleptic drugs, had Clinical Global Impression Scale of moderately ill, had Brief Psychiatric Rating Scale total of at least 45 **Motivation:** Not reported	**Intervention 1:** Clozapine (600mg/day) **Intervention 2:** Clozapine (300mg/day) **Control:** Clozapine (100mg/day) **Outcome:** Plasma cotinine levels (ng/ml)	+ **Limitations:** Type II error (lack of power), only within group tests performed
McEvoy 1995 RCT, n=12	**Location:** USA **Setting:** In-patient	DSM-III-R criteria for chronic schizophrenia, smoked cigarettes, clinically hospitalised for substantial persistent psychopathology **Motivation:** Not reported	**Intervention 1:** Clozapine (high plasma range, 350-450 ng/ml) **Intervention 2:** Clozapine (medium plasma range, 200-300ng/ml) **Control:** Clozapine (low plasma range, 50-150ng/ml) **Outcome:** Number of cigarettes smoked per day, expired CO levels	- **Limitations:** Very small sample size, baseline expired CO levels lower in low plasma group as compared to intervention groups, no measure of abstinence, short follow-u
McEvoy 1999 Randomised BA, n=55 smokers	**Location:** USA **Setting:** Unclear (seems like in-patient)	DSM-III-R criteria for schizophrenia, all previously failed to respond to adequate trials of at least 2 conventional antipsychotic medications **Motivation:** Not reported	**Intervention 1:** Clozapine (high plasma range, 350-450 ng/ml) **Intervention 2:** Clozapine (medium plasma range, 200-300ng/ml) **Control:** Clozapine (low plasma range, 50-150ng/ml) **Outcome:** Research staff counted number of cigarette butts smoked by participation during 120 minutes of free available cigarette smoking cessation, expired CO level, serum nicotine and cotinine levels at end of 120 minute session	+ **Limitations:** Small sample size in whom serum nicotine and cotinine were measured, no stratification by smoking status, short follow-up

FLUOXETINE

Fluoxetine is an antidepressant from the selective serotonin reuptake inhibitor (SSRI) class.

Cornelius 1997 (RCT, USA, +) A RCT was conducted to assess the effectiveness of fluoxetine in 25 in-patients of a psychiatric hospital diagnosed with co-morbid major depression (severe to very severe levels) and alcohol dependence. Participants were randomised to receive fluoxetine (20mg capsule, increasing to 2 capsules after 2 weeks if substantial residual depression symptoms persisted) or placebo, for 12 weeks. All participants received usual care as outpatients following discharge from the hospital, which comprised of weekly supportive psychotherapy sessions.

SMOKING CESSATION OUTCOMES

The study demonstrated self-reported number of cigarettes smoked per day was fewer in the fluoxetine group compared to placebo (mean 16.2 versus 22.3 cigarettes/day) across the 12 weeks; however, the difference when comparing the treatment groups was not statistically significant.

EVIDENCE STATEMENT

Fluoxetine is an antidepressant from the selective serotonin reuptake inhibitor (SSRI) class. It has been suggested that antidepressant, such as fluoxetine, may be effective for smoking cessation.

ES6.1 There is weak evidence from one trial (**Cornelius 1997 [RCT, USA, +]**) of 25 in-patients with major depression suggested fluoxetine (40mg/day) had no significant effect on the number of cigarettes smoked per day in the short term.

The evidence from the individual study on fluoxetine as a smoking cessation medication is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. The study was conducted in participants with co-morbid alcohol dependence in the USA.

Table 6 Summary evidence table for fluoxetine

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Cornelius 1997 RCT, n=25	**Location:** USA **Setting:** In-patient	Co-morbid depression and alcohol dependence, DSM-III-R, 10+ cigarettes per day **Motivation:** Not reported	**Intervention:** Fluoxetine, one capsule (20mg/day), could be increased to 2 capsules per day after 2 weeks if substantial residual depressive symptoms persisted (however, this was rare). **Control:** Placebo capsule **Outcome:** Self-reported number of cigarettes per day	+ **Limitations:** Modest sample size, lack of long term follow-up, self-reported outcome

GALANTAMINE

Galantamine is an alkaloid that is used for the treatment of mild to moderate Alzheimer's disease and other memory impairments.

Kelly 2008 (RCT, USA, -) A RCT was conducted to assess the effectiveness of galantamine in 86 smoking or non-smoking participants with schizophrenia or schizoaffective disorders who were being treated either as in-patients or outpatients. Participants were randomised to galantamine (initial dose of 8mg/day given twice daily with an increase of 8mg/day every 4 weeks to a maximum dose of 24mg/day) or a matching placebo, for 12 weeks.

SMOKING CESSATION OUTCOMES

The study demonstrated at the end of the 12 weeks that smokers who were randomised to galantamine (n=18) had non-significantly different expired CO levels to smokers randomised to placebo (n=24) (p=0.40). Additionally, no significant difference was seen in the number of cigarettes smoked at the end of the 12 weeks between the two treatment groups (p=0.11).

EVIDENCE STATEMENT

Galantamine is an alkaloid that is used for the treatment of mild to moderate Alzheimer's disease and other memory impairments. It has been suggested that galantamine may be useful for smoking cessation.

ES7.1 There is very weak evidence from one RCT of 42 inpatients and outpatients with schizophrenia (**Kelly 2008 [RCT, USA, -]**) of no effect of galantamine (maximum dose of 24mg/day) on self-reported and objective markers of cigarette use in the short term.

The evidence from the individual study on galantamine as a smoking cessation medication is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. The study was conducted in the USA.

Table 7 Summary evidence table for galantamine

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Kelly 2008 RCT, n=43 smokers	**Location:** USA **Setting:** In-patient and outpatient	Smokers, DSM-IV diagnosis for schizophrenia or schizoaffective disorder, 18-60 years of age, chronically stable, antipsychotic agent other than clozapine, Simpson-Angus Extrapyramidal symptoms score≤4 **Motivation:** Not reported	**Intervention:** Galantamine (max 24mg/day) **Control:** Placebo **Outcome:** Number of cigarettes smoked per day, expired CO levels	- **Limitations:** Lack of objective measure of abstinence, lack of bio-verified outcome, randomised smokers and non-smokers, small sample size, excluded participants from analysis that did not adhere to randomised medication

NALTREXONE

Naltrexone is an opioid receptor antagonist which is used in alcohol dependence and opioid dependence.

Szombathyne-Meszaros 2010 (RCT, USA, +) A RCT was conducted to assess the effectiveness of naltrexone in 79 outpatients diagnosed with schizophrenia or schizoaffective disorders with co-morbid alcohol dependence. Participants were randomised to receive oral naltrexone at an equivalent dose of 50mg/day (100mg on Monday's, 100mg on Wednesday's, and 150mg on Friday's), or placebo, for 12 weeks.

SMOKING CESSATION OUTCOMES

No significant difference was seen in the proportion of participant's achieving cessation at the end of 12 weeks between the naltrexone and placebo groups (2/41 versus 2/38). Additionally, no significant differences were seen in the number of cigarettes smoked per day from baseline to week 12 between the naltrexone and placebo groups; however, significantly lower numbers of cigarettes were smoked within each treatment group from baseline to week 12 (naltrexone, baseline: 126 versus end of trial: 101 cigarettes/day; placebo, baseline: 121 versus end of trial: 103 cigarettes/day).

EVIDENCE STATEMENT

Naltrexone is an opioid receptor antagonist which is used for the treatment of alcohol dependence and opioid dependence.

ES8.1 There is moderate evidence from one RCT in 79 outpatients diagnosed with schizophrenia or schizoaffective disorders with co-morbid alcohol dependence that naltrexone (50g/day) had no significant effect on abstinence or self-reported numbers of cigarettes smoked per day (**Szombathyne-Meszaros 2010 [RCT, USA, +]**).

The evidence from the individual study on naltrexone as a smoking cessation medication is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. The study was conducted in participants with co-morbid alcohol dependence in the USA.

Table 8 Summary evidence table for naltrexone

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Szombathyne-Meszaros 2010 RCT, n=79	**Location:** USA **Setting:** Outpatient	Schizophrenia or schizoaffective disorder with co-morbid alcohol and nicotine dependence **Motivation:** Not reported	**Intervention:** Naltrexone (50mg/day) **Control:** Placebo **Outcome:** Smoking cessation, number of cigarettes smoked adjusted for baseline	+ **Limitations:** Insufficient methodological details in abstract

NICOTINE REPLACEMENT THERAPY

Dalack 1999 (NRCT, USA, -) A non-randomised cross-over trial was conducted to assess the effectiveness of NRT in 10 in-patients of a general psychiatry unit who were diagnosed with schizophrenia or schizoaffective disorders. Participants received either a NRT patch (22mg/24hr) or a placebo patch on the morning of day 1, and were left to smoke as much as they preferred, with measurements being taken in the afternoon. On day 2, study personnel replaced the patch with the same treatment condition and the protocol followed that of day 1. After a five day wash-out period, participants received the other condition on days 8 and 9, following the same protocol as one day 1.

SMOKING CESSATION OUTCOMES

The study demonstrated that while the mean expired CO levels decreased by 15% during the active compared to the placebo patch condition, this was not statistically significant (p=0.14). Additionally, similar numbers of cigarettes were smoked per day on NRT compared to placebo (mean 25.3 versus 26.1 cigarettes per day).

Hartman 1991 (RCT, USA, ++) A randomised cross-over controlled trial was conducted to assess the effectiveness of NRT in 3 in-patients and 11 outpatients who were receiving psychiatric services. Participants were randomised to receive a 24μl solution containing either 30% nicotine base (8mg) or water (placebo). The solutions were applied in the morning and covered with a polyethylene wrap and secured with surgical tape. Participants were instructed to smoke as much of their preferred brand of cigarettes as they wanted for 7 hours, and the number of cigarettes smoked was observed and recorded by study personnel. One week later the participants received the other solution.

SMOKING CESSATION OUTCOMES

The study demonstrated participants smoked significantly less cigarettes during the 7 hour period when they were wearing the nicotine patch compared to placebo patch (mean 9.9 versus 11.8 cigarettes smoked, p<0.04).

Chou 2004 (RCT, China, -) A RCT was conducted to assess the effectiveness of NRT in 68 participants with schizophrenia attending a day care ward at a psychiatric hospital. Participants were randomised to receive NRT patch (14mg/day for weeks 1-6, decreasing to 7mg/day for weeks 7-8), or a control group, for 8 weeks.

SMOKING CESSATION OUTCOMES

The study demonstrated significantly greater reductions in the NRT patch group from the end of the first week of patch use for expired CO levels (p<0.0001) and self-reported number of cigarettes smoked per day (p<0.001), and continued being reduced through to 3 months follow-up (CO levels, p<0.0001; self-reported number of cigarettes smoked per day, p<0.0001) compared to placebo. Additionally, point prevalence abstinence (bio-verified by CO<10ppm) were higher in the NRT patch group (26.9%) as compared to placebo (0%) at 3 months follow-up.

Williams 2007 (RCT, USA, +) A RCT was conducted to assess the effectiveness of high dose NRT in 51 outpatients diagnosed with schizophrenia or schizoaffective disorders. Participants were randomised to high dose NRT (42mg patch), or standard dose (21mg patch), for 8 weeks.

SMOKING CESSATION OUTCOMES

The study reported no significant difference in 7 day point prevalence abstinence between the high dose and standard dose treatment groups at 8 weeks (8/25 versus 6/26; p=0.48). Additionally, time to first relapse back to smoking was reported to be not significantly different between the treatment groups.

Hill 2007 (NRCT, USA, -) A non-randomised pilot study was conducted to assess the effectiveness of adding nicotine replacement therapy to CBT in 9 participants with major depressive disorders who were interested in smoking cessation. CBT was given to both treatment groups and consisted of 8 weekly group sessions lead by the study physician. The group sessions last for 60 minutes each and were focused on monitoring of thoughts, daily activities, interpersonal contacts, and mood. The intervention group additionally received nicotine replacement therapy (14mg) patches daily for 8 weeks. The target quit date was set for 8 days post start of CBT, and follow-ups were monitored monthly.

SMOKING CESSATION OUTCOMES

The study demonstrated no significant difference between the treatment groups on the number of cigarettes smoked per day at 3 months follow-up.

Thorsteinsson 2001 (RCT, USA, +) A randomised mixed-design controlled trial was conducted which assessed the effectiveness of NRT patches in 38 outpatients with un-medicated major depression who were motivated to quit. The participants were randomised to NRT patches (21mg/24hr) for 2 weeks followed by placebo for one week, or placebo patches for 2 weeks followed by placebo for 1 week. The placebo patches contained 22mg of nicotine but has a barrier to prevent absorption. The participants were allowed to smoke for the first 8 days of the study at the end of which the target quit date was set, followed by 14 days of the assigned intervention, followed by 7 days of placebo, and 6 days of follow-up, thus the total length of the study was 29 days.

SMOKING CESSATION OUTCOMES

The study demonstrated self-reported abstinence was significantly more likely in the NRT group compared to the placebo group (78% versus 50%; one sided $p<0.05$) at day 29. No significant interaction was detected on the average total withdrawal ratings (assessed using the Nicotine symptoms Checklist and Hughes-Hatsukami Withdrawal Questionnaire).

EVIDENCE STATEMENTS

ES9.1 There is moderate evidence from one trial (**Hartman 1991 [RCT, USA, ++]**) to suggest NRT (8mg given once) is effective for smoking reduction in the very short term (7 hours follow-up) in 14 in-patients and outpatients with psychiatric disorders.

ES9.2 There is weak evidence from one trial (**Williams 2007 [RCT, USA, +]**) to suggest there is no significant benefit in smoking cessation from using high dose NRT (42mg patch) compared to standard dose NRT (21mg patch) in the short term in 51 outpatients with schizophrenia.

ES9.3 There is mixed very weak evidence from two trials (**Dalack 1999 [NRCT, USA, -]; Chou 2004 [RCT, China, -]**) regarding the effectiveness of standard dose NRT (22mg/24hr or 14mg/day) for smoking reduction or cessation in schizophrenia, where a significant decrease in mean expired CO levels was seen on the day following the patch application, but no reduction in the number of cigarettes smoked in one trial (**Dalack 1999 [NRCT, USA, -]**). In the other trial (**Chou 2004 [RCT, China, -]**), significant reductions in expired CO levels, self-reported number of cigarettes smoked per day and point prevalence abstinence (bio-verified by CO<10ppm) were seen in the NRT patch compared to placebo.

ES9.4 There is mixed weak evidence from two trials (**Thorsteinsson 2001 [RCT, USA, +]; Hill 2007 [NRCT, USA, -]**) regarding the effectiveness of standard dose NRT (21mg/24hr or 14mg/day) for smoking reduction or cessation in major depression, where smoking cessation was significantly more likely in the short term in one study (**Thorsteinsson 2001 [RCT, USA, +]**), but no significant difference was seen in the number of cigarettes smoked in the short term in the other study (**Hill 2007 [NRCT, USA, -]**).

The evidence from the studies on NRT is applicable to the UK setting as the study was predominately based on outpatient populations with mental health disorders, and the intervention reflects current clinical prescribing practice in the UK for smoking cessation, and could be feasible within populations with mental health disorders. The studies were conducted predominately in the USA, with a further study being conducted in China.

Table 9 Summary evidence table for NRT

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Chou 2004 RCT, n=68	**Location:** China **Setting:** Unclear	18+ years, 15+ cigarettes per day for at least one years, at least 45.4 kg weight **Motivation:** Not reported	**Intervention:** NRT patch (14 mg/day) **Control:** No description **Outcome:** Continuous and point prevalence abstinence (bio-verified by CO<10ppm), expired CO levels, self-reported cigarettes per day	- **Limitations:** Almost completely male smoker, small sample size, short follow-up, insufficient details regarding population of control group. Control group had no intervention
Dalack 1999 NRCT, n=10	**Location:** USA **Setting:** Outpatient	DSM-III-R criteria for schizophrenia or schizoaffective disorder, moderate to severe nicotine dependence, absence of current non-nicotine substance use disorder, no history of serious medical illness **Motivation:** Not trying to cut down or quit	**Intervention:** NRT patch (22mg/day) **Control:** Placebo patch **Outcome:** Self-reported number of cigarettes per day, expired CO levels	- **Limitations:** Population not trying to cut down or quit, short follow-up, small sample size, not randomised
Hartman 1991 RCT, n=14	**Location:** USA **Setting:** In-patient and outpatient	Psychiatric patients voluntary receiving psychiatric service, smoked at least 10 cigarette per day, free of substantial cardiovascular disease and pulmonary disease, no current substance use disorder **Motivation:** Did not have to indicate any desire to quit	**Intervention:** 24μl solution containing 30% nicotine base (8mg) **Control:** 24μl solution containing water **Outcome:** Observed number of cigarette butts smoked	++ **Limitations:** Very short follow-up, lack of bio-verified outcome
Hill 2007 NRCT, n=9	**Location:** USA **Setting:** Outpatient	Smokers, aged 22-65 years, smoked at least 15 cigarettes per day, with major depressive disorder **Motivation:** Interested in smoking cessation	**Intervention:** NRT patches (14mg/day) + CBT **Control:** Not treatment + CBT **Outcome:** Self-reported number of cigarettes smoked per day	- **Limitations:** Small sample size, lack of randomisation, high attrition, lack of objective outcome, short term follow-up
Thorsteinsson 2001 RCT, n=38	**Location:** USA **Setting:** Outpatient	18+ years of age, un-medicated outpatient, cigarette smoker with major depression without psychotic features as specified in the DSM-III-R, ≥14 on Hamilton Rating Scale for Depression, ≥1 cigarette pack/day for at least one year, biochemically confirmed	**Intervention:** NRT patches (21mg/day) **Control:** placebo patch **Outcome:** Self-reported smoking, withdrawal	+ **Limitations:** Drop-out rate substantially higher in placebo (50%) than intervention group (22%), underpowered study, lack of objective measure of

		CO≥15ppm, willingness to comply with study demands **Motivation:** Motivation to quit,		abstinence, short follow-up
Williams 2007 RCT, n=51	**Location:** USA **Setting:** Outpatient	Participants with schizophrenia or schizoaffective disorder **Motivation:** Wanted to quit smoking	**Intervention:** NRT patch (42mg/day) **Control:** NRT patch (21mg/day) **Outcome:** Point prevalence abstinence (7 day), time to first relapse to smoking	+ **Limitations:** Insufficient information in abstract regarding population and methods, short follow-up, small sample size

VARENICLINE

Dutra 2012 (UBA, USA, -) An uncontrolled before and after study was conducted to assess the effectiveness of varenicline in 102 outpatients diagnosed with schizophrenia or schizoaffective disorder, who were willing to set a quit date within the next 2-3 weeks. All participants received varenicline at a dose of 0.5mg per day for three days, then 0.5mg twice/day for four days, and 1mg twice/day for 11 weeks. Patients also received group cognitive behavioural therapy intended to promote smoking cessation for 12 weekly one-hour sessions.

SMOKING CESSATION OUTCOMES

The study demonstrated 60.4% achieved 14-day point prevalence abstinence at 12 weeks (bio-verified with CO<9ppm).

Panchas 2012 (UBA, USA, -) An uncontrolled before and after study was conducted to assess the effectiveness of varenicline in 112 outpatients diagnosed with schizophrenia or schizoaffective disorder, who had a desire to quit smoking. All participants received varenicline at a dose of 0.5mg per day for three days, then 0.5mg twice/day for four days, and 1mg twice/day for 11 weeks. Patients also received weekly one-hour manualised cognitive behavioural therapy for smoking cessation which had been tailored for people with schizophrenia.

SMOKING CESSATION OUTCOMES

The study demonstrated 47.3% achieved at least 2 weeks continuous abstinence and 34% achieved at least 4 weeks continuous abstinence at week 12 (bio-verified with CO<9ppm). Significant reductions in expired CO levels were also demonstrated from baseline to week 12 ($p<0.01$).

Smith 2009 (UBA, USA, -) An uncontrolled before and after study was conducted to assess the effectiveness of varenicline in 14 male in-patients and outpatients diagnosed with schizophrenia or schizoaffective disorders, of which most did not have a strong preference to definitely cease smoking. All participants received no intervention for 3 to 4 weeks before treatment commenced. Varenicline was given at doses for 0.5-1mg/day during the first week of treatment, increasing to 1mg twice/day for weeks 2-5 of treatment. Doses could be reduced if necessary to 1mg/day for side effects. Participants then received no interventions for 3 weeks.

SMOKING CESSATION OUTCOMES

The study demonstrated no significant difference in the number of cigarettes smoked per day between the before and after phases of the trial (mean, 36.5 versus 12.5 cigarettes/day; $p=0.12$). However, significant differences were seen between the before and after phases of the trial for expired CO levels (mean 8.97 versus 4.85ppm; $p=0.005$) and plasma cotinine levels (mean, 238.6 versus 129.8; $p=0.001$).

Weiner 2011a (RCT, USA, +) A randomised controlled pilot trial was conducted to assess the effectiveness of varenicline in 9 outpatients who had symptomatic schizophrenia or schizoaffective disorders. Participants were randomised to varenicline (1mg twice per day), or placebo, for 12 weeks. All of the participants received individual smoking cessation counselling. Participants had two counselling session before starting study treatments at week 0. The target quit date was following their week 1 visit at the end of the third counselling session.

SMOKING CESSATION OUTCOMES

The study demonstrated no significant difference in continuous abstinence (weeks 8-12, bio-verified with expired CO) between the participants taking varenicline compared to placebo (75% versus 0%; p=0.14). However, expired CO levels were significantly lower in the varenicline group compared to placebo after 4 weeks of medication till the end of the trial (p=0.02).

EVIDENCE STATEMENTS

ES10.1 There is weak evidence from four trials (**Dutra 2012 [UBA, USA, -]; Panchas 2012 [UBA, USA, -]; Smith 2009 [UBA, USA, -]; Weiner 2011a [RCT, USA, +]**) that varenicline (2mg/day), in predominately outpatients with schizophrenia or schizoaffective disorders, may reduce smoking consumption, where significant reductions were seen in expired CO levels in three studies (**Panchas 2012 [UBA, USA, -]; Smith 2009 [UBA, USA, -]; Weiner 2011a [RCT, USA, +]**); however, no significant difference was seen in continuous abstinence (bio-verified by expired CO) in one trial as compared to placebo (**Weiner 2011a [RCT, USA, +]**).

The evidence from four studies on varenicline is directly applicable to the UK setting as the intervention reflects current clinical prescribing practice in the UK for smoking cessation, and could be feasible within populations with mental health disorders. All of the four studies studies were conducted in the USA.

Table 10 Summary evidence table for varenicline

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Dutra 2012 UBA, n=102	**Location:** USA **Setting:** Outpatient	DSM-IV criteria for schizophrenia or schizoaffective disorder by SCID interview and chart review, clinically stable, stable dose of antipsychotic medication for at least one month, not acutely at risk of suicide, at least 10 cigarettes smoked per day for 6 months, expired CO level>9ppm or salivary cotinine>20ng/ml **Motivation:** Willing to set a quit date within the next 2-3 weeks	**Intervention:** Varenicline (2mg/day) **Control:** Baseline, no intervention **Outcome:** 14 day point prevalence at 12 weeks	- **Limitations:** Small sample size, concurrent administration of varenicline and cognitive behavioural therapy, no control group, concurrent medications for schizophrenia
Pacras 2012 UBA, n=112	**Location:** USA **Setting:** Outpatient	DSM-IV,-TR diagnosis of schizophrenia or schizoaffective disorder, smoked at least 10 cigarettes per day, stable dose of antipsychotic medication for at least one month, expired CO>9ppm **Motivation:** Desire to quit smoking	**Intervention:** Varenicline (2mg/day) **Control:** Baseline, no intervention **Outcome:** At least 2 weeks biochemically verified continuous abstinence, at least 4 weeks biochemically verified continuous abstinence, at 12 weeks	- **Limitations:** Small sample size, no control group, many participants terminated treatment early (33%)
Smith 2009 UBA, n=14	**Location:** USA **Setting:** In-patient and outpatient	Schizophrenia or schizoaffective disorder, long history of smoking cigarettes **Motivation:** Agreed to trial antismoking drug for cigarette	**Intervention:** Varenicline (2mg/day) **Control:** Baseline, no intervention **Outcome:** Number of cigarettes smoked per day, expired CO levels	- **Limitations:** Small sample size, lack of direct placebo control, in-patient hospital setting with smoking restrictions, lack of

		smoking habit although most did not have a strong personal desire to definitely stop smoking		uniformly strong desire to quit smoking, lack of randomisation, short follow-up, lack of abstinence outcome
Weiner 2011a RCT, n=9	**Location:** USA **Setting:** Outpatient	DSM-IV-TR criteria for schizophrenia or schizoaffective disorder for over 3 years, clinically stable, but still symptomatic, regular smoker at least 10 cigarettes smoked per day, smoked for at least one year, FTND score≥4 **Motivation:** Not reported	**Intervention:** Varenicline (2mg/day) **Control:** Placebo **Outcome:** Continuous smoking abstinence (week 8-12, bio-verified by CO≤10ppm), expired CO levels	+ **Limitations:** Small sample size

COMBINATION PHARMACOTHERAPIES

NICOTINE REPLACEMENT THERAPY AND BUPROPION

Saxon 2003 (NRCT, USA, -) A non-RCT was conducted to assess the effectiveness of NRT as compared to bupropion and the combination of NRT and bupropion in 115 outpatients who were diagnosed with an Axis 1 psychiatric disorder who were motivated to quit smoking. Eligible psychiatric disorders included PTSD, major depression, psychotic disorder, bipolar, and other anxiety disorders; 75% of participants additionally had substance dependence. Participants attended a smoking cessation program consisting of weekly group sessions followed by weekly group sessions with expired CO monitoring, and were expected to attend a minimum of 8 sessions. The content of the sessions focused on psycho-education and relapse prevention. Treatment assignment (no pharmacotherapy, NRT patches [21mg/day], bupropion SR [150mg/day for 3 days increasing to 150mg twice/day], or combination of the two was given based on the participants and clinicians' preferences, with the dosage adjusted to participant's response and side effects.

SMOKING CESSATION OUTCOMES

The study demonstrated participants who received the combination treatment were significantly more likely to have a greater reduction in the self-reported number of cigarettes smoked per day ($p=0.004$) and expired CO levels ($p<0.001$) than compared to the other treatment groups.

Culhane 2008 (RCT, USA, -) The findings from two RCTs were amalgamated and reported to assess the effectiveness of NRT in combination with bupropion in a total of 114 outpatients diagnosed with schizophrenia or schizoaffective (depressive type) disorders, who were willing to set a quit date within four weeks of enrolment. All participants received 12 weekly sessions of CBT as part of a smoking cessation group programme. Participants were randomised to receive bupropion SR (150mg twice per day); a combination of bupropion SR (150mg twice a day) and NRT patch (21mg/day for 4 weeks, decreasing to 7mg/day for 2 weeks, then 7mg/day for 2 weeks; additionally, 2mg of NRT gum could be used as required up to 9 pieces per day); or placebo. The placebo group also consisted of an extra 10 participants who were not medically eligible for bupropion SR (and thus could not be randomised), but who received open NRT patches and CBT as describe above.

SMOKING CESSATION OUTCOMES

The amalgamated findings from the two studies reported no significant differences in continuous abstinence (weeks 9-12, bio-verified by CO<9ppm) between the treatment groups; however, a re-analysis focusing on comparing the combination group and placebo groups, found the combination of bupropion and NRT patches were significantly more likely to be abstinent (weeks 9-12, bio-verified by CO<9ppm) compared to placebo (OR 9.16, 95% CI 1.02-82.2; $p=0.04$); however, no significant difference in abstinence (week 9-12, bio-verified by CO<9ppm) was detected for single treatment of bupropion or NRT patches compared to placebo (OR 5.27, 95% CI 0.64-43.2; $p=0.16$).

George 2008 (RCT, USA, ++) A RCT was conducted to assess the effectiveness of bupropion given in combination with nicotine replacement therapy in 59 outpatient participants with schizophrenia

or schizoaffective disorders. All participants received nicotine replacement therapy patches (21mg/24 hours) which were applied at day 15 to coincide with the target quit date. Participants were randomised to receive bupropion SR (initially 150mg/day orally once a day for 3 days, increasing to 150mg twice a day), or a matching placebo, until day 70.

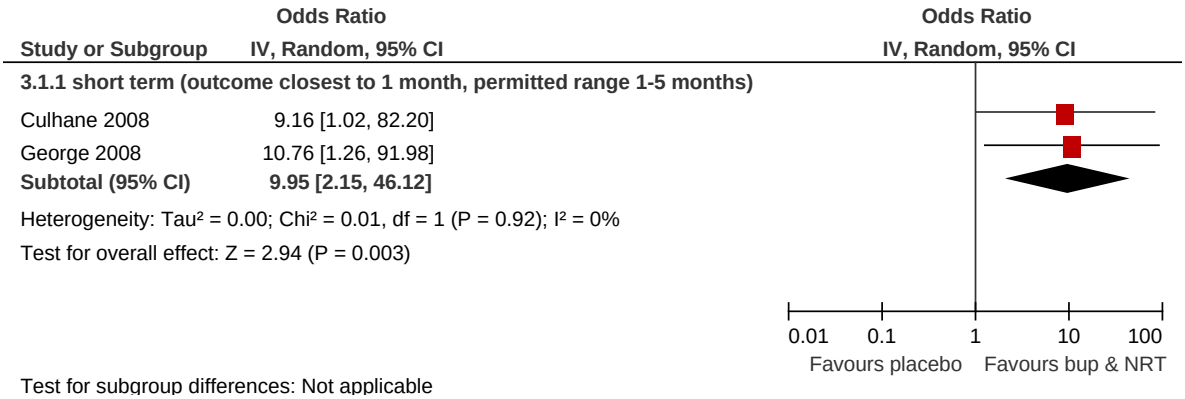
SMOKING CESSATION OUTCOMES

The study demonstrated participants randomised to bupropion were significantly more likely to achieve continuous abstinence (days 43 to 70, bio-verified by expired CO) compared to the placebo group (27.6% versus 3.4%; OR 10.76, 95% CI 1.24 to 91.98; p<0.03). However, in terms of long term point prevalence abstinence at day 70, no significant difference was seen between the groups (13.8% versus 0%; p=0.11).

META-ANALYSIS FOR COMBINATION OF NICOTINE REPLACEMENT THERAPY AND BUPROPION

A random effects meta-analysis was conducted to assess the pooled effects of the combination of bupropion and NRT on smoking cessation. The pooled result from two trials demonstrated the combination of bupropion and NRT was significantly effective for short term smoking cessation (pooled OR 9.95, 95% CI 2.15-46.12, I^2=0%; Figure 7).

Figure 7 **Meta-analysis of combination of bupropion and NRT for smoking cessation in schizophrenia**



EVIDENCE STATEMENTS

ES11.1 There is very weak evidence from one trial (**Saxon 2003 [NRCT, USA, -]**) to suggest the combination of bupropion (300mg/day) and NRT (21mg/day) is effective for reducing smoking consumption and expired CO levels compared to mono-therapy or no pharmacotherapy in 115 psychiatric outpatients in the short term.

ES11.2 There is moderate evidence from a pooled analysis of two trials (**George 2008 [RCT, USA, ++]; Culhane 2008 [RCT, USA, -]**) to suggest the combination of bupropion (300mg/day) and NRT (21mg/day) is effective for smoking cessation in the short term in outpatients with schizophrenia (Pooled OR 9.95, 95% CI 2.15-46.12). However, there is moderate evidence from one trial (**George 2008 [RCT, USA, ++]**) to suggest the combination of bupropion (300mg/day) and NRT (21mg/day) is not effective for smoking cessation in the long term in 59 outpatients with schizophrenia.

The evidence from the studies based on the combination treatment of bupropion with NRT is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. All of the studies were conducted in the USA.

Table 11 Summary evidence table for combination of bupropion with NRT

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Culhane 2008 RCTs, n=not reported	**Location:** USA **Setting:** Outpatient	Adults with schizophrenia or schizoaffective disorder (depressive type), DSM-IV criteria, stable symptoms, stable dose of antipsychotic medication for 30 days, smoked 10+ cigarettes per day **Motivation:** Willing to set quit date within 4 weeks of enrolment	**Intervention 1:** Bupropion SR (300mg/day) + CBT **Intervention 2:** Bupropion SR (300mg/day) + CBT + NRT patch (initiated on quit date) 21 mg/day for 4 weeks, decreasing to 14mg/day for 2 weeks, decreasing to 7 mg/day for 2 weeks). NRT gum (2mg used a required up to 9 pieces per day) **Control:** Placebo (no further description). **Outcome:** Continuous abstinence (week 9-12, bio-verified by CO<9ppm)	- **Limitations:** Small sample size, small number achieving continuous abstinence, not generalisable to larger population of outpatients with schizophrenia who are trying to stop smoking, short follow-up, methods unclear, influence of extra 10 participants not clear
Saxon 2003 UBA, n=115	**Location:** USA **Setting:** Outpatient	Dual diagnosis of alcohol and drug dependence, 74.8% had Axis I psychiatric diagnosis in addition to substance dependence **Motivation:** Motivated to quit but not required to set a target quit date	**Intervention:** Compares NRT, bupropion and combination of NRT and bupropion, no doses or lengths of treatment described, doses based on response and side effect experience **Control:** N/A **Outcome:** Self-reported number of cigarettes smoked per day, expired CO levels	- **Limitations:** Lack of control group, heterogeneity of participants in regards to baseline diagnoses and medications, non-blinded treatment assignment, lack of data on drop outs, lack of randomisation, short follow-up, insufficient information regarding doses of treatments given
George 2008 RCT, n=59	**Location:** USA **Setting:** Outpatient	SCID-IV criteria for schizophrenia or schizoaffective disorder, nicotine dependence, 10+ cigarettes per day, CO≥10ppm, clinically stable, total PANSS score<70 at study entry, stable	**Intervention:** Bupropion (300mg/day) + NRT patches (21mg/day) + smoking cessation therapy **Control:** Placebo + NRT patches (21mg/day) + smoking cessation therapy **Outcome:** Continuous abstinence (day 43-70), point prevalence abstinence (day 70 and 6 months)	++ **Limitations:** Small sample size, lack of applicability to typical outpatient smoker with schizophrenia since participants were highly motivated to quit

		dose of antipsychotic medication for at least one month and continued on same medication during trial **Motivation:** Baseline motivation quit scale indicating willingness to quit in next 30 days or less on contemplation ladder		

COMBINATION OF BEHAVIOURAL THERAPIES AND PHARMACOTHERAPIES

HIGH INTENSITY BEHAVIOURAL THERAPY AND BUPROPION

Weiner 2001 (UBA, USA, -) An uncontrolled before and after study was conducted to assess the effectiveness of bupropion with high intensity behavioural support for smoking reduction in 9 outpatients diagnosed with schizophrenia or schizoaffective disorders. Following a 2 week stabilisation period where no treatment was delivered, participants then received 9 weekly sessions of group therapy, and adjunctive bupropion therapy SR was started on the third week of group therapy (dose of 150mg once/day for 3 days, increasing to 150mg twice/day for 12 weeks), over a 14 week period.

SMOKING CESSATION OUTCOMES

The study demonstrated a significant decrease in expired CO levels from baseline to week 14 (mean, 39.4 versus 18.4ppm; $p<0.05$).

EVIDENCE STATEMENT

ES12.1 There was very weak evidence from one trial (**Weiner 2001 [UBA, USA, -]**) to suggest the combination of high intensity behavioural therapy with bupropion significantly reduced smoking consumption in 9 outpatients with schizophrenia from baseline to short term follow-up (mean expired CO levels reduced from 39.4 to 18.4 ppm).

The evidence from the individual study on the combination of high intensity behavioural therapy with bupropion is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. The study was conducted in the USA.

Table 12 Summary evidence table for combination of high intensity behavioural therapy with bupropion

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Weiner 2001 UBA, n=9	**Location:** USA **Setting:** Outpatient	DSM-IV schizophrenia or schizoaffective disorder, medically stable, stable cigarette smoking habits, high nicotine dependence **Motivation:** Expressed interest in decreasing their smoking,	**Intervention:** 14 week treatment period – 9 sessions of weekly group therapy + bupropion (300mg/day) **Control:** 2 week stabilisation period (baseline) **Outcome:** Expired CO levels	- **Limitations:** Small sample size, open-label design, lack of strict inclusion criteria regarding smoking consumption, lack of randomisation, lack of control group, lack of abstinence as an outcome, incorrect statistical analysis performed

HIGH INTENSITY BEHAVIOURAL THERAPY AND NICOTINE REPLACEMENT THERAPY

Baker 2006 (RCT, Australia, +) A RCT was conducted to assess the effectiveness of a high intensity behavioural therapy programme with NRT in 298 in-patients and outpatients with a diagnosis of a non-acute psychotic disorder (57% had schizophrenia or schizoaffective disorders), who had an interest in quitting smoking. The high intensity behavioural therapy programme consisted of 8 one hour individual sessions on motivational interviewing and CBT, and participants randomised to this group could also use NRT (21mg for 6 weeks, decreasing to 14mg for 2 week, then 7mg for 2 weeks) in addition to the treatment given to the control group. Participants in the control group receive treatment as usual which included access to their general practitioner and publicly funded community health teams; additionally, participants received booklets on smoking cessation.

SMOKING CESSATION OUTCOMES

The study demonstrated no significant difference between the high low intensity behavioural therapy programme with NRT and the low intensity programme on continuous abstinence (bio-verified by expired CO<10ppm) at three months (OR 2.95, 95% CI 0.83-10.53), 6 months (OR 2.84, 95% CI 0.48-16.67), or 12 months (OR 5.28, 95% CI 0.31-90.20) follow-up. Similar non-significant findings were seen for 7 day point prevalence abstinence (3 months, OR 2.78, 95% CI 0.96-8.07; 6 months, OR 2.54, 95% CI 0.70-9.28; 12 months, OR 1.72, 95% CI 0.58-5.09). However, participants in the high intensity programme with NRT were significantly more likely to have reduced their smoking by 50% or more relative to baseline at 3 months (OR 3.89, 95% CI 1.9-7.89) and 12 months (OR 2.09, 95% CI 1.03-4.27); but no significant effect was seen at 6 months follow-up (OR 1.88, 95% CI 0.92-3.82).

Baker 2009 (NRCT, Australia, -) A non-randomised uncontrolled before and after study was conducted to assess the effectiveness of motivational interviewing, CBT, plus NRT in 48 outpatients with a diagnosis of a non-acute psychotic disorder (79% had schizophrenia or schizoaffective disorders). Following the baseline phase of the trial, participants received 6 weekly sessions (1 hour duration each) and 3 fortnightly booster sessions, of a healthy lifestyle intervention programme which used motivational interviewing and CBT delivered individually to participants. Additionally, up to 42mg NRT was provided by per day. Follow-up was at a mean of 19.6 weeks following the commencement of treatment.

SMOKING CESSATION OUTCOMES

The study demonstrated significant reductions in the number of cigarettes smoked per day from baseline to post-treatment assessment (mean 30.8 versus 17.2; p<0.001). 11.6% of the participants were continuously abstinent (bio-verified with expired CO levels<10ppm), and 18.6% achieved 7 day point prevalence abstinence, from quit date to the post-treatment assessment.

Barnett 2008 (RCT, USA, +) A RCT was conducted to assess the cost-effectiveness of a high intensity behavioural intervention with NRT in 322 outpatients with a current diagnosis of uni-polar depression who were being treated for their disorder. Participants were randomised to either a high

intensity behavioural therapy programme with NRT (dose not stated) (programme called 'stepped care'), or brief contact, and assessed over an eighteen month period. The stepped care programme initially consisted of three scheduled assessments to identify which participants were ready to quit smoking. Once participants were identified as contemplating quitting, or wanted treatment, 6 sessions of psychological counselling and up to 10 weeks of NRT patches were given. In those who continued to smoke after this treatment, participants were offered bupropion and two additional counselling sessions. Participants in the control group received a printed stop smoking guide and a list of smoking cessation programme.

SMOKING CESSATION OUTCOMES

The study demonstrated participants who received stepped care were more likely to be abstinent from smoking at the end of the 18 months follow-up than those in the brief contact group (7 day point prevalence, bio-verified by CO<10ppm) 24.6% versus 19.1%; p value not reported).

EVIDENCE STATEMENTS

ES13.1 There is moderate evidence from one trial of 298 in-patients and outpatients with a diagnosis of non-acute psychotic disorders (**Baker 2006 [RCT, Australia, +]**) to suggest high intensity behavioural therapy (CBT with motivational interviewing) in addition to NRT (21mg/day) resulted in no significant effect on continuous smoking abstinence (bio-verified by CO<10ppm) at short (OR 2.95, 95% CI 0.83-10.53), medium (OR 2.84, 95% CI 0.48-16.67) and long (OR 5.28, 95% CI 0.31-90.20) term follow-ups.

ES13.2 There is weak evidence from two trials in participants with a diagnosis of non-acute psychotic disorders (**Baker 2006 [RCT, Australia, +]; Baker 2009 [NRCT, Australia, -]**) that high intensity (CBT with motivational interviewing) in addition to NRT (21mg/day or up to 42mg/day) reduced self-reported cigarette consumption. In one trial (**Baker 2006 [RCT, Australia, +]**) a 50% or more reduction in cigarette consumption was seen in the short (OR 3.89, 95% CI 1.9-7.89) and long (OR 2.09, 95% CI 1.03-4.27) term, but not at medium term follow-up (OR 1.88, 95% CI 0.92-3.82). In the other trial (**Baker 2009 [NRCT, Australia, -]**) a significant reduction in the number of cigarettes smoked per day was seen from baseline to short term follow-up (mean reduction from 30.8 to 17.2 cigarettes/day).

ES13.3 There is weak evidence from one trial of 322 outpatients with a diagnosis of depression (**Barnett 2008 [RCT, USA, +]**) to suggest high intensity behavioural support in addition to NRT (dose not stated) (and an offer of bupropion in those who continued to smoke) resulted in a higher proportion of participants being abstinent at long term follow-up (7 day point prevalence, bio-verified by CO<10ppm, 24.6% versus 19.1%, p value not reported).

The evidence from the studies on the combination of high intensity behavioural therapy with NRT is directly applicable to the UK setting as the intervention reflects current clinical prescribing practice

in the UK for smoking cessation, and could be feasible within populations with mental health disorders. Two of the studies were conducted in Australia which has a similar smoking treatment service to the UK; the remaining study was conducted in the USA.

Table 13 Summary evidence table for combination of high intensity behavioural therapy with NRT

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Baker, 2006 RCT, n=298	**Location:** Australia **Setting:** Outpatient	Smokers with non-acute psychotic disorders, 18+ years, 15+ cigarettes per day, ICD 10 diagnosis of psychotic disorder **Motivation:** not reported	**Intervention:** Eight one hour individual sessions of motivational interviewing and CBT plus NRT in addition to treatment as usual **Control:** Treatment as usual included access to general practitioner and publicly funded community health teams **Outcome:** Continuous abstinence (bio-verified by expired CO<10ppm), point prevalence smoking abstinence, smoking reduction	+ **Limitations:** No control for therapy time
Baker 2009 UBA, n=48	**Location:** Australia **Setting:** Outpatient	18+ years, 15+ cigarettes per day, ICD 10 diagnosis of non-acute psychotic disorder **Motivation:** Not reported	**Intervention:** Nine sessions of treatment programme based on healthy lifestyle intervention with motivational interviewing **Control:** Pre-treatment programme baseline, no intervention	- **Limitations:** Absence of control group, no longer term follow-up, UBA study, different length of time for before and after phases
Barnett 2008 RCT, n=322	**Location:** USA **Setting:** Outpatient	Current diagnosis of uni-polar depressions, smoked at least one cigarette per day **Motivation:** Participants did not need to be interested in quitting smoking	**Intervention:** Stepped care: Six sessions of psychological counselling and up to 10 weeks of NRT with dermal patch. Those who continued to smoke after this treatment were offered bupropion SR and two additional counselling sessions **Control:** Brief contact: receive printed top-smoking guide and a list of smoking cessation programmes from the smoking study staff **Outcome:** Point prevalence abstinence (7 day, bio-verified by CO<10ppm)	+ **Limitations:** Insufficient methods about the trial was the paper focuses on cost-effective rather than effectiveness of treatment

COMBINATION OF CONTINGENCY PAYMENTS AND PHARMACOTHERAPIES

CONTINGENCY PAYMENTS AND BUPROPION

Tidey 2011 (RCT, USA, ++) A randomised controlled four-arm trial was conducted to assess the effectiveness of contingency payments in addition to bupropion SR in 57 outpatients with a diagnosis of schizophrenia or schizoaffective disorder, who indicated they planned to quit smoking in the next 6 months. Participants were randomised to receive either contingency payments with bupropion (n=12), contingency payment with placebo (n=16), non-contingent payment with bupropion (n=11), or non-contingent payment with placebo (n=13). Contingency payments comprised of a $25 US gift card for attendance and an additional cash bonus of $5 US could be earned if urinary cotinine levels were reduced by 25% to the previous sample given or if the reading was <80ng/ml. Non-contingent payments comprised of a $25 US store card for attending the session and providing a urine sample, an additional cash bonus of $5 US was given regardless of the results of the urinary cotinine levels measured in the sample. Participants randomised to bupropion were given bupropion SR 150mg/day orally for days 1-3, increasing to 150mg/day twice a day orally for days 4-22. A matching placebo was given orally for 22 days.

SMOKING CESSATION OUTCOMES

Bupropion did not significantly reduce smoking by itself or increase the effectiveness of the contingent payment intervention. However, the study did report that participants receiving contingent payments had lower cotinine levels ($p<0.001$), lower expired CO levels ($p<0.01$), and reduced number of cigarettes smoked per day ($p<0.01$) compared to non-contingent payments at weeks 3 and 4 compared to weeks 1 and 2. No significant difference was detected between the treatment groups for cigarette craving (Questionnaire on Smoking Urges, $p<0.05$).

EVIDENCE STATEMENT

ES14.1 There is moderate evidence from one trial (**Tidey 2011 [RCT, USA, ++]**) to suggest contingency payments given in addition to bupropion (300mg/day) did not significantly reduce smoking, or have a detrimental effect on cigarette craving, in 57 outpatients with schizophrenia.

The evidence from the individual study on the combination of contingency payments with bupropion is potentially applicable to the UK as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. The study was conducted in the USA.

Table 14 Summary evidence table for combination of contingency payments with bupropion

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Tidey 2011 RCT, n=57	**Location:** USA **Setting:** Outpatient	DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder, 18+ years of age, 20+ cigarettes per day, FTND score≥6, clinically stable psychoactive medication for at least 2 months **Motivation:** 4+ score on contemplation ladder indicating some interest in quitting in next 6 months	**Intervention 1:** Contingency payment with bupropion (300mg/day) **Intervention 2:** Contingency payment with placebo **Intervention 3:** Non-contingent payment with bupropion (300mg/day) **Control:** Non-contingency payment with placebo **Outcome:** Number of cigarettes smoked in past week, cotinine levels	++ **Limitations:** Short treatment period, small sample size, self-reported compliance of medication

CONTINGENCY PAYMENTS AND NICOTINE REPLACEMENT THERAPY

Tidey 2002 (NRCT, USA, -) A non-randomised within-subject repeated measures design was conducted to assess the effectiveness of monetary payments for smoking reduction with NRT in 17 outpatients diagnosed with schizophrenia or schizoaffective disorders, who were not actively trying to quit smoking during the study. Three conditions were tested within the participants; i) contingency payment with NRT patch (21mg/24 hours); ii) contingency payment with placebo patch; iii) non-contingent payment with placebo patch. The sequence of assignment to the three conditions was ordered across the participants to ensure similar numbers of participants were exposed to the conditions at each phase of the study. The patch condition was applied the day before the contingency payment condition was commenced, and participants received $10 US for attending this visit. Visits were then made three times a day for the next 5 days. Participants in the contingency payment condition who met the cut-off for expired CO levels≤11ppm at each visit received $3 US for their first reading, increasing by $0.50 for each subsequent reading below the cut-off, with a bonus $10 US for every third consecutive reading below the cut-off. Thus, the maximum total available cash that could be received was $147.50 US. Participants in the non-contingent payment condition receive $9.80 per visit regardless of their expired CO levels, so that the total cash received for this condition match that from the contingency payment condition.

SMOKING CESSATION OUTCOMES

The study demonstrated significantly different mean expired CO level between the three conditions (mean, contingency payment with NRT 19.4ppm versus contingency payment with placebo 20.5ppm versus non-contingent payment with placebo 28.0ppm; $p<0.05$). Post-hoc analyses indicated significantly higher expired CO levels in the non-contingent payment with placebo group than compared to contingency payment with placebo or contingency payment with NRT; however, no significant differences were seen between the contingency payment conditions with NRT and contingency payment with placebo. Salivary cotinine levels were significantly different between the three conditions ($p<0.05$); with post-hoc analyses revealing significantly higher levels in the non-contingent payment with placebo and contingency payment with NRT compared to contingent payment with placebo. Significant differences in nicotine withdrawal was seen between the three conditions with significantly lower levels being observed in the non-contingent payment with placebo condition than compared to the other two conditions (assessed using the Minnesota Nicotine Withdrawal Scale). No significant differences between the conditions was seen for anticipation of immediate positive outcome from smoking subscale and for anticipation of relief from negative affect relating to nicotine withdrawal subscale (Questionnaire on Smoking Urges).

Gallagher 2007 (RCT, USA, -) A randomised controlled three-arm trial was conducted to assess the effectiveness of contingency payments in addition to NRT in 180 outpatients who had schizophrenia or schizoaffective disorder that resulted in long term illness. Participants didn't have to commit to quitting, but 48% expressed an interest, and 50% were interested in reducing smoking consumption. Participants were randomised to contingency payments with NRT, contingency payments only, or a minimal self-quit intervention group. Contingency payments comprised of the participants earning $25 US for completing the baseline and follow-up visits, and $5 US for each regular visit; additionally, they could earn bonus payments for each visit if their expired CO level was <10ppm ($20 US for weeks 2-4, $40 US for bimonthly visits week 6-12, $60US for monthly visits weeks 16-24, and $80 US for follow-up visit at week 36; total of 12 visits). NRT patches were given at a dose of 21mg for 16 weeks from baseline. The self-quit intervention group had a minimal (brief advice) intervention which comprised of 3 visits, in which they were encouraged to use available community resources and received smoking cessation literature focusing on tobacco and cessation related education and motivational support, and were allowed to use NRT patches (21mg for 16 weeks).

SMOKING CESSATION OUTCOMES

The study demonstrated abstinence (bio-verified by expired CO≤10ppm) at week 20 was significantly more likely in participants receiving contingency payments (OR 11.59, 95% CI 3.23-41.61) and participants receiving contingency payments with NRT (OR 13.73, 95% CI 3.85-49.03) compared to the self-quit intervention group (p=0.001). Similar significant findings were also seen at week 36 (contingency payments, OR 4.37, 95% CI 1.49-12.81; contingency payments with NRT, OR 7.87, 95% CI 2.72-22.79; compared to self-quit intervention group, p=0.001). However, when abstinence was bio-verified by saliva cotinine levels (<15ng/ml), contradictory findings were reported where no significant difference was seen at week 20 (p=0.08) or at week 36 (p=0.92); however, it should be noted that salivary cotinine levels are higher than a non-smokers when NRT patches are used, therefore this is not an optimal method of bio-verification in this instance. Reduced smoking (based on cotinine levels, but definition of thresholds were not clear) was significantly more likely at week 20 in the contingency payment and contingency payment with NRT groups compared to self-quit intervention group (32% versus 12% versus 4%; p=0.02); however, no significant effect was seen at week 36.

EVIDENCE STATEMENTS

ES15.1 There is very weak mixed evidence from one trial of 180 outpatients with schizophrenia or schizoaffective disorders (**Gallagher 2007 [RCT, USA, -]**) regarding the effectiveness of contingency payments, given in addition to NRT (21mg/day), on abstinence compared to self-quit interventions in the short term and at medium term. Significant increases in smoking cessation were observed when abstinence was bio-verified by CO≤10ppm (short term, OR 13.73, 95% CI 3.85-49.03; medium term, OR 7.87, 95% CI 2.72-22.79). No significant effects were seen when abstinence was bio-verified by saliva cotinine<15ng/ml at short term or medium term follow-up; however, it should be noted that salivary cotinine levels are higher than a non-smokers when NRT patches are used, therefore this is not an optimal method of bio-verification in this instance.

ES15.2 There is very weak evidence from one trial of smoking reduction (**Tidey 2002 [NRCT, USA, -]**) to suggest contingency payments with NRT patches resulted in significantly reduced levels of cigarette/tobacco consumption in 17 outpatients with schizophrenia (measured using expired CO and salivary cotinine levels), but did not have an effect on the anticipation of an immediate positive outcome from smoking or on relief of nicotine withdrawal symptoms.

The evidence from the studies on the combination of contingency payments with NRT is potentially applicable to the UK setting as the intervention may be feasible to the UK setting; however, this does not reflect current clinical prescribing practice in the UK. Both studies were conducted in the USA.

Table 15 Summary evidence table for combination of contingency payments with NRT

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Gallagher 2007 RCT, n=180	**Location:** USA **Setting:** Outpatient	DSM-IV criteria for Axis I psychotic spectrum or affective disorder that resulted in long term illness, significant symptoms and functional impairments due to disorder. 18+ years, 10+ cigarettes per day, smoked for at least 3 years, expired CO>10ppm, saliva cotinine>15ng/ml, orally English **Motivation:** Didn't have to commit to quitting but 48% expressed an interest, and 50% were interested in reducing smoking consumption	**Intervention 1:** Contingent payment (earned progressively more money for each visit is expired CO<10ppm, $25 US for completing baseline and follow-up visits, and $5 US per regular visit, maximum of $580 US over the trial) **Intervention 2:** Contingent payment (as above) with NRT patches (21mg) **Control:** Self-quit (minimal intervention) **Outcome:** Point prevalence abstinence (bio-verified by expired CO≤10ppm)	- **Limitations:** Attrition high, quit rates low, small sample size, non-blinding of research staff and outcome assessors, length of treatment varied between intervention and control groups, those on NRT patches were told not to use patch if returned to smoking
Tidey 2002 NRCT (within participant), n=17	**Location:** USA **Setting:** Outpatient	Schizophrenia or schizoaffective disorder confirmed by board-certified psychiatrist, regular smoker, CO≥18ppm **Motivation:** Not actively trying to quit during study	**Intervention 1:** Contingency payments for smoking reduction with NRT patch (21mg/24 hours). Maximum total payment possible was $147.50 US **Intervention 2:** Contingency payments for smoking reduction with placebo patch. Maximum total payment possible was $147.50 US **Control:** Non-contingent payment and placebo patch. Participants received $9.80 US for each visit regardless of CO reading **Outcome:** Smoking reduction (bio-verified by CO≤11ppm)	- **Limitations:** Short term outcomes, small sample size, lack of randomisation

QUESTION 1B. HOW EFFECTIVE ARE INTERVENTIONS FOR TEMPORARY ABSTINENCE IN HELPING PEOPLE FROM THE POPULATION OF INTEREST?

No studies were identified which assessed the effectiveness of interventions for temporary abstinence in the population of interest.

EVIDENCE STATEMENT

ES16.1 No studies were identified which assessed the effectiveness of interventions for temporary abstinence in people with mental health illness.

SUBSIDIARY QUESTION 1A I) HOW DOES THE EFFECTIVENESS OF SMOKING CESSATION AND TEMPORARY ABSTINENCE INTERVENTIONS VARY BY MENTAL HEALTH DIAGNOSIS, GENDER, SEXUAL ORIENTATION, AGE, ETHNICITY, RELIGION, SOCIOECONOMIC STATUS, DISABILITY, AND BY POPULATIONS OF INTEREST (INCLUDING PATIENTS, HOUSEHOLD MEMBERS, VISITORS AND STAFF)?

The included studies only reported findings for two of the above categories, mental health diagnosis and age. All of the included studies assessed the effectiveness of smoking cessation treatments in patients, none of them focused on household members, visitors or staff.

MENTAL HEALTH DIAGNOSIS

The majority of the studies included in the review assessed the effectiveness of interventions for smoking cessation in participants with schizophrenia or schizoaffective disorders. Only a few studies looked at the effectiveness of interventions in different subgroups (PTSD [3 studies], bipolar [1 study], or major depression [4 studies]). None of the included studies directly compared the effectiveness in different populations; therefore further analysis of specific interventions by mental health diagnosis was not performed due to substantial differences in the protocols of the included studies.

AGE

All of the included studies except one looked at adult mental health populations; however none of these reported the effectiveness of treatments broken down into age categories. Only one study included in the review used a non-adult mental health population.

Brown 2003 (RCT, USA, +) assessed the effectiveness of motivational interviewing in 191 psychiatric in-patients aged 13-17 years who smoked at least one cigarette per week, using a RCT design. Eligible diagnoses included mood (n=84), anxiety (n=105), disruptive behaviour (n=150), and substance related (n=136) disorders (participants could have dual disorders); however, participants with current psychotic disorders were excluded. Participants were randomised to motivational interviewing or brief advice. The motivational interviewing group comprised two 45-minute individual therapy sessions during hospitalization. Following discharge patients were offered NRT patches if they desired to quit smoking and smoked 10+ cigarettes per day. The brief advice group received 5-10 minutes of smoking cessation advice by the study therapist and a self-help pamphlet, and following discharge they were also offered NRT patches if they desired to quit and smoked 10+ cigarettes per day.

SMOKING CESSATION OUTCOMES

The study demonstrated no significant difference between the treatment groups on the number of cigarettes smoked per day at 12 months follow-up (p=0.74). Additionally, 7 day point prevalence (bio-verified with expired CO<10ppm and saliva cotinine<15ng/ml) was not significantly difference at one month (11.0% versus 11.0%), 6 months (13.3% versus 8.5%), or 2 months (14.0% versus 9.9%) follow-up (all p>0.30). Over the 12 month follow-up, no significant difference was seen in the odds of abstinence between the treatment groups (OR 1.16, 95% CI 0.59-2.31; p=0.38); however, the study reported having an anxiety disorder was associated with a higher odds of abstinence (OR 4.71, 95% CI 2.19-10.12; p=0.0001). On discharge, participants in the motivational interviewing group had significantly higher self-efficacy (confidence in ability to refrain from smoking) compared to those receiving brief advice (p=0.04).

EVIDENCE STATEMENT

ES17.1 No studies were identified which assessed the differential effectiveness of smoking cessation interventions by mental health diagnosis, gender, sexual orientation, ethnicity, religion, socioeconomic status, disability, or in populations of interest other than patients (for example, household members, visitors or staff).

ES17.2 There is very weak evidence from one trial (**Brown 2003 [RCT, USA, -]**) to suggest high intensity behavioural therapy with NRT had no overall significant effect on smoking cessation in 191 adolescent psychiatric in-patients at short term and long (OR 1.16, 95% CI 0.59-2.31) term outcome timings.

The evidence from the individual study on high intensity behavioural therapy in adolescents is potentially applicable to the UK as there is no reason to assume that the interventions could not be implemented in UK outpatient and in-patient settings.

SUBSIDIARY QUESTION 1A II) ARE THERE DIFFERENCES IN THE EFFECTIVENESS OF SMOKING CESSATION AND TEMPORARY ABSTINENCE INTERVENTIONS BY DELIVERER, TIMING (OR POINT IN THE CARE PATHWAY), FREQUENCY, DURATION, AND SEVERITY OF DEPENDENCE, AND SETTING IN WHICH THE INTERVENTION IS ASSESSED, FOR EXAMPLE IN-PATIENTS VERSUS OUT-PATIENT?

The included studies only allowed for sensitivity analyses based on the setting in which the interventions were assessed, and the type of anti-psychotic medication used.

SETTING IN WHICH THE INTERVENTION IS ASSESSED

The majority of the included studies looked at out-patients populations (30 studies), 10 assessed in-patients population only, and three assessed the interventions in in-patients and outpatients. The setting was unclear in 6 of the included studies. However, comparisons in effectiveness of interventions could not be performed due to the differences in protocols between the studies which solely assessed in-patients and those assessing outpatients. In the three studies which assessed in-patients and outpatients the results were not compared between the two sub-populations.

TYPE OF ANTI-PSYCHOTIC MEDICATION USED

HIGH INTENSITY BEHAVIOURAL THERAPY

One study compared the effectiveness of the high intensity behavioural therapy by the type of anti-psychotic medication being used to treat schizophrenia or schizoaffective disorders.

George 2000 (quasi-RCT, USA, +) A quasi-RCT was conducted to assess the effectiveness of a specialised schizophrenia group therapy programme as compared to a standard therapy programme in 45 participants with schizophrenia or schizoaffective disorders who were motivated to quit smoking. All participants were given nicotine replacement therapy patches (21mg/24hr) for 6 weeks starting on the target quit date (week 3), decreasing to 14mg weeks 7-10, and 7mg weeks 11 and 12. The intervention group received weekly group therapy for 10 weeks, which was based on 3 weeks of motivational enhancement therapy, followed by 7 weeks of psycho-education, social skills training, and relapse prevention strategies. The control group received 7 weeks of manualised behaviour group therapy and supportive group counselling during the 3 remaining weekly group sessions, with each session lasting 60 minutes.

SMOKING CESSATION OUTCOMES

When comparing cessation outcomes according to patients' antipsychotic treatment regime, the study demonstrated that those taking atypical antipsychotic medication were significantly more likely to achieve abstinence at 12 weeks than compared to those on typical antipsychotic medication (55.6% versus 22.2%; $p<0.01$); however, the potential interaction between therapy programme assignment and type of antipsychotic medication was not statistically assessed.

BUPROPION

Three studies compared the effectiveness of the bupropion by the type of antipsychotic medication being used to treat schizophrenia or schizoaffective disorders.

Evins 2005 (RCT, USA, ++) A RCT was conducted to assess the effectiveness of bupropion in 57 outpatients diagnosed with schizophrenia or schizoaffective disorders, who were willing to set a smoking quit date. Participants were randomised to bupropion (150mg/day for 7 days, if medication was tolerated well, then dose increased to 150mg twice/day for 11 weeks), or placebo, for 12 weeks. All participants received 12 weekly sessions of CBT.

SMOKING CESSATION OUTCOMES

The study reported there was no significant effect of antipsychotic medications were seen on abstinence outcomes (atypical versus typical); however, no formal statistical assessment on the interaction between bupropion and type of antipsychotic medication was reported.

Evins 2007 (RCT, USA, ++) A RCT was conducted which assessed the effectiveness of bupropion in 51 outpatients diagnosed with schizophrenia, who were willing to set a smoking quit date. Participants were randomised to receive bupropion (150mg per day for 7 days, increasing to twice daily for 11 weeks), or placebo (using the regimen as the active group), for 12 weeks. All participants additionally received 12 one hour weekly smoking cessation programme sessions. Following setting a target quit date; all participants received NRT patches (21mg/day for 4 weeks, decreasing to 14mg/day for 2 weeks, decreasing to 7mg/2 weeks). NRT gum (2mg) was used as needed up to a maximum dose of 18mg/day.

SMOKING CESSATION OUTCOMES

No significant differences in continuous abstinence outcomes (bio-verified by CO) were seen by the type of antipsychotic medication being used by the participants (typical versus atypical).

George 2002 (RCT, USA, ++) A RCT was conducted to assess the effectiveness of bupropion in 32 outpatients with schizophrenia or schizoaffective disorders who expressed the desire to quit smoking. Participants were randomised to bupropion SR (initial dose 150mg orally daily for 3 days

increasing to 150mg orally twice per day), or matching placebo, for 10 weeks. All participants additionally received smoking cessation group therapy for 10 weeks on a weekly basis with each session lasting 60 minutes. The target quit date was during the 3rd group therapy session on week 3.

SMOKING CESSATION OUTCOMES

A subgroup analysis based on the type of antipsychotic medication was being used by the participants (atypical [ATP] or typical [TYP]) revealed those on atypical antipsychotic medication who received bupropion were significantly more likely to quit smoking at week 10 (bio-verified by CO<10ppm) as compared to the other groups (bupropion + ATP 66.7% versus bupropion + TYP 0% versus placebo +ATP 20% versus placebo + TYP 0%; p<0.01).

EVIDENCE STATEMENT

ES18.1 There is weak evidence from one trial (**George 2000 [quasi-RCT, USA, +]**) to suggest the effectiveness of high intensity behavioural therapy for smoking cessation was not significantly related to the type of antipsychotic medication used in schizophrenia.

ES18.2 There is contradictory strong evidence from three trials (**George 2002 [RCT, USA, ++]; Evins 2005 [RCT, USA, ++]; Evins 2007 [RCT, USA, ++]**) regarding the difference in effectiveness of bupropion for smoking cessation by the type of antipsychotic medication used in schizophrenia.

The evidence from the studies is potentially applicable to the UK as the interventions are feasible within the UK setting.

SUBSIDIARY QUESTION 1A III) WHAT ARE THE ADVERSE EVENTS AND OTHER CONSEQUENCES ASSOCIATED WITH USING SMOKING CESSATION AND TEMPORARY ABSTINENCE INTERVENTIONS IN THE POPULATIONS OF INTEREST?

ADVERSE EVENTS

Adverse events were primarily reported in studies which assessed the effectiveness of a pharmacological medication; however, not all trials assessing pharmacological intervention reported adverse events. Only 21 of the studies included in the review reported details regarding adverse events, which are categorised into behavioural and pharmacological interventions, and summarised below.

ADVERSE EVENTS RELATING TO HIGH INTENSITY BEHAVIOURAL THERAPY INTERVENTIONS

Only one of the studies included in the review assessed the adverse events of high intensity behavioural therapy for smoking cessation.

POST-TRAUMATIC STRESS DISORDER

McFall 2010 (RCT, USA, ++) reported no significant differences were observed between the integrated care or usual standard of care groups in 943 outpatients under PTSD care (p=0.49), relating to psychiatric hospitalisations, life-threatening or potentially jeopardising psychiatric conditions not resulting in hospitalisation, and cardiac or gastrointestinal related events.

EVIDENCE STATEMENT

ES19.1 There was moderate evidence from one trial (**McFall 2010 [RCT, USA, ++]**) to suggest smoking cessation arising from using high intensity behavioural therapy does not result in any adverse effects relating to psychiatric hospitalisation, cardiac or gastrointestinal related events in 943 outpatients with PTSD.

This evidence is applicable to the UK setting.

ADVERSE EVENTS RELATED TO BUPROPION

Twelve studies included in the review assessed the adverse events of bupropion.

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

Bloch 2010 (RCT, Israel, –) assessed the effectiveness of bupropion (300mg) in 61 outpatients with a diagnosis of schizophrenia or schizoaffective disorder. The study did not report adverse events in the paper; however the authors stated that participant drop out was not related to side effects.

Evins 2001 (RCT, USA, +) assessed the effectiveness of bupropion (150mg) in 18 outpatients diagnosed with schizophrenia. The study reported there were no serious adverse events during the trial.

Evins 2005 (RCT, USA, ++) assessed the effectiveness of bupropion (300mg) in 57 outpatients diagnosed with schizophrenia or schizoaffective disorders. The study reported three serious adverse events during the trial which required discontinuation of study treatment. One participant had an allergic reaction to bupropion resulting in hives, urticaria, and wheezing. Two participants in the placebo group experienced suicide ideation during the trial.

Evins 2007 (RCT, USA, ++) assessed the effectiveness of bupropion (300ng) in 51 outpatients diagnosed with schizophrenia. The study reported that no serious adverse events were seen during the trial; however 4 participants stopped their assigned medication due to adverse events (2 participants in bupropion group [1 in week 4 for insomnia, 1 in week 9 for dizziness]; 2 participants in placebo group [1 in week 2 for insomnia and palpitations, 1 in week 11 for insomnia, indigestion and weight loss]).

Fatemi 2005 (RCT, USA, –) assessed the effectiveness of bupropion (dose unknown) for smoking reduction in 10 outpatients with a diagnosis of schizophrenia or schizoaffective disorders. The study reported there were decreases in side effect symptoms in both the active and placebo phases of the trial as compared to baseline measurements.

George 2002 (RCT, USA, ++) assessed the effectiveness of bupropion (300mg) in 32 outpatients with schizophrenia or schizoaffective disorders. The study reported the experience of dry mouth was significantly more likely in the bupropion group compared to placebo (62.5% versus 25.0%, $p<0.05$); however, no significant difference were seen for headache, difficulty falling asleep, memory problems, blurred vision, irregular heartbeat, nausea, diarrhoea, anxiety/agitation, or tremor.

George 2008 (RCT, USA, ++) assessed the effectiveness of bupropion (300mg) (given in combination with NRT patches [21mg]) in 59 participants with schizophrenia or schizoaffective disorders. The study reported significant increases in side effects in the bupropion group as compared to placebo, relating to lack of concentration, jitteriness, light headedness, muscle stiffness, frequent nocturnal wakening. Additionally, 3 serious adverse events involving psychotic decompensation (2 placebo, 3 bupropion); however, these events were deemed to be unrelated to the study medication.

Li 2009 (RCT, China, –) assessed the effectiveness of bupropion (300mg) in 69 male in-patients diagnosed with schizophrenia. The paper reported significantly higher numbers of side effects in the bupropion group as compared to placebo ($p<0.05$), primarily relating to insomnia, dry mouth, restlessness, headache, nausea, diaphoresis (excessive sweating).

Tidey 2011 (RCT, USA, ++) assessed the effectiveness of bupropion (300mg) in addition to contingency payments in 57 outpatients diagnosed with schizophrenia or schizoaffective disorders. The study reported no significant differences between the bupropion and placebo groups for the following events all reported at least once by the participants; insomnia (41% versus 57%), restlessness (50% versus 46%), dry mouth (54% versus 38%), anxiety (36% versus 54%), headache (41% versus 38%), nausea (41% versus 31%), diarrhoea (23% versus 39%), chest pain (27% versus 19%), blurred vision (18% versus 15%), memory problems or confusion (19% versus 12%), racing heartbeat (9% versus 12%). Most events were mild to moderate in severity. Other events occurred <5%. No seizures of suicidal behaviours were noted.

Weiner 2011b (RCT, USA, ++) assessed the effectiveness of bupropion (300mg) in 46 outpatients diagnosed with schizophrenia or schizoaffective disorders. The study reported five participants in the bupropion group had adverse events relating to restlessness/anxiety (2 participants at week 1), mild exacerbations of psychosis (1 participant at baseline), rash (1 participants at week 2), and seizure due to hyponatraemia (low sodium concentration in serum of the blood) (1 participant at week 13). Two participants in the placebo group had adverse events relating to worsening of anxiety and restlessness (1 participant at week 4), and non-specific complaints of sedation and malaise (general uneasiness).

Post-traumatic stress disorder

Hertzberg 2001 (RCT, USA, +) assessed the effectiveness of bupropion (300mg) in 15 male combat veterans with a primary diagnosis of PTSD. The study reported adverse events in one participant randomised to bupropion relating to ataxia (lack of voluntary coordination of muscle movements), headaches, and jitteriness.

Bipolar disorder

Weiberger 2008 (RCT, USA, –) assessed the effectiveness of bupropion (300mg) in 5 outpatients with a diagnosis of bipolar. The study reported one of the participants (placebo) had increased distractibility and sexual inappropriateness; and another participant (placebo) had difficulty sleeping and increased energy. However, no side effects were reported in the participants on bupropion.

EVIDENCE STATEMENTS

ES20.1 There is strong evidence from 10 trials (**George 2002 [RCT, USA, ++]; Weiner 2011b [RCT, USA, ++] ; Bloch 2010 [RCT, Israel, –]** ; **Evins 2007 [RCT, USA, ++]; Evins 2005 [RCT, USA, ++]; Evins 2001 [RCT, USA, +] ; Li 2009 [RCT, China, –]**; **Tidey 2011 [RCT, USA, ++]; Fatemi 2005 [RCT, USA, -]; George 2008 [RCT, USA, ++]**) to suggest that bupropion was well tolerated in participants diagnosed with schizophrenia or schizoaffective disorders, with expected side effects of bupropion being seen (relating to dry mouth, nausea and headaches).

ES20.2 There is weak evidence from one trial (**Hertzberg 2001 [RCT, USA, +]**) to suggest bupropion was well tolerated in 15 male outpatients with PTSD.

ES20.3 There is very weak evidence from one trial (**Weinberger 2008 [RCT, USA, –]**) to suggest bupropion was well tolerated in 5 outpatients diagnosed with bipolar disorder.

Adverse events related to the use of bupropion are likely to be applicable to the UK setting, as there are no reasons to assume otherwise.

ADVERSE EVENTS RELATING TO NRT

Six studies, categorized by population, included in the review reported adverse events relating to NRT use.

MENTAL HEALTH DISORDER

Hartman 1991 (RCT, USA, ++) assessed the effectiveness of NRT patches in 3 in-patients and 11 outpatients receiving care from psychiatric services using a cross-over design. No differences in irritation at the patch site, taste or smell were noted in the participants.

Saxon 2003 (NRCT, USA, –) assessed the effectiveness of NRT patches (21mg) given in combination with bupropion (300mg) in 115 outpatients diagnosed with an axis I psychiatric disorder. Adverse events were not formally collected by the study; however, 3 participants reported adverse events when using NRT relating to i) dizziness, shortness of breath and chest pain, ii) light headedness, chest pain and nausea, iii) dizziness and disorientation.

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

George 2000 (quasi-RCT, USA, +) assessed the effectiveness of NRT (21mg) given in combination with high intensity behavioural therapy in 45 participants with schizophrenia or schizoaffective disorders. The study reported no significant differences in medication side effects of NRT between the treatment groups over the 6 weeks of use.

Dalack 1999 (NRCT, USA, +) assessed the effectiveness of NRT patches (22mg) in 10 in-patients diagnosed with schizophrenia or schizoaffective disorder using a cross-over design. The study reported one participant had nausea which was self-limiting whilst on the placebo condition. No side effects were noted during the NRT condition.

Williams 2007 (RCT, USA, +) assessed the effectiveness of high dose NRT patches (42mg) compared to standard patch (21mg) in 51 outpatients with a diagnosis of schizophrenia or schizoaffective disorders, for 8 weeks. The abstract reported high dose and standard dose NRT patches were tolerated well by the participants.

Tidey 2002 (NRCT, USA, –) assessed the effectiveness of contingency payments with NRT patches (21mg) for smoking reduction in 17 outpatients diagnosed with schizophrenia or schizoaffective disorders. The study reported itchiness or irritability at the patch site in 6 participants during the active NRT patch condition; however 5 of these participants also reported itchiness or irritability during the placebo patch condition. Problems sleeping or unusual dreams were reported in 4 participants during the contingency payment with NRT condition; and only one of these participants reported this event during the placebo condition too. One participant reported tiredness, cramping of the arm, and nausea. The study reported no evidence of nicotine toxicity even though the participants continued to smoke while wearing the patch.

EVIDENCE STATEMENT

ES21.1 There is moderate evidence from four trials (**George 2000 [quasi-RCT, USA, +]; Dalack 1999 [NRCT, USA, +]; Williams 2007 [RCT, USA, +]; Tidey 2002 [NRCT, USA, –]**) to suggest standard dose NRT patches (21 or 22mg/day) are well tolerated in participants with schizophrenia or schizoaffective disorders, with expected side effects being reported (irritability at patch site).

ES21.2 There is weak evidence from one trial (**Williams 2007 [RCT, USA, +]**) to suggest high dose NRT patches (42mg/day) are well tolerated in schizophrenia and schizoaffective disorder.

ES21.3 There is weak evidence from two trials (**Hartman 1991 [RCT, USA, ++]; Saxon 2003 [NRCT, USA, –]**) to suggest NRT patches (8mg/day are well tolerated in participants with mental health disorders.

Adverse events related to the use of NRT are applicable to the UK setting as there is no reason to assume that this would not be the case.

ADVERSE EVENTS RELATING TO VARENICLINE

Three of the four studies included in the review reported adverse events in the trial.

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

Panchas 2012 (UBA, USA, -) assessed the effectiveness of varenicline with weekly cognitive behavioural therapy in 112 outpatients with schizophrenia or schizoaffective disorders. The study reported nausea was common; however, there 12 cases of serious adverse events leading to discontinuation of medication relating to nausea (5 participants), anxiety (1 participant), weight gain (1 participant), depressed mood (1 participant), paranoid (1 participant), suicide ideation (1 participant),and non-tobacco substance use (1 participant)

Smith 1999 (UBA, USA, –) assessed the effectiveness of varenicline in 14 male in-patients and outpatients diagnosed with schizophrenia or schizoaffective disorders. The study reported no adverse events; however, side effects were common, where two participants withdrew consent during the study due to side effects of varenicline. Throughout the study, 8 participants complained at least once of nausea, vomiting, shaking, dry mouth, tiredness-sleepiness, and cramps.

Weiner 2011a (RCT, USA, +) assessed the effectiveness of varenicline in 9 outpatients with schizophrenia or schizoaffective disorders. The study reported no adverse events; however, side effects were common. Side effects relating to constipation (2 participants), insomnia (3 participants), and nausea (3 participants) were reported in the varenicline group; and insomnia (1 participants), and nausea (1 participants) were reported in the placebo group.

EVIDENCE STATEMENT

ES22.1 There is weak evidence from three trials (**Panchas 2012 [UBA, USA, -]; Smith 1999 [UBA, USA, -]; Weiner 2011a [RCT, USA, +]**) to suggest varenicline did not lead to side effects in participants with schizophrenia or schizoaffective disorders; however, side effects were common, relating to nausea and insomnia.

Adverse events related to the use of varenicline are likely to be applicable to the UK setting as there is no reason to assume that this would not be the case.

ADVERSE EVENTS RELATING TO COMBINATION TREATMENT OF BUPROPION AND NRT

One of the trials included in the review reported on the adverse events relating to combination of bupropion and NRT.

MENTAL HEALTH DISORDER

Saxon 2003 [NRCT, USA, –] assessed the effectiveness of the combination of bupropion (300mg) and NRT patches (21mg) in 115 outpatients with an axis I psychiatric disorder. Adverse events were not formally collected by the study; however, no adverse events were reported for the combination treatment.

EVIDENCE STATEMENT

ES23.1 There is very weak evidence from one trial (**Saxon 2003 [NRCT, USA, -]**) to suggest combination treatments of bupropion and NRT patches are well tolerated in major mental health disorders (axis I psychiatric disorders).

Adverse events related to the use of the combination of bupropion with NRT are likely to be applicable to the UK setting as there is no reason why this would not be the case.

UNINTENDED CONSEQUENCES, INCLUDING MENTAL HEALTH RELATED OUTCOMES

Unintended consequences, including outcomes referring to participants' mental health condition, were reported in 28 studies which are categorised into behavioural and type of pharmacological medication, and summarised below.

HIGH INTENSITY BEHAVIOURAL THERAPY INTERVENTIONS

Five studies included in the review assessed the impact of unintended consequences of high intensity behavioural therapy interventions.

MENTAL HEALTH DISORDERS

Currie 2008 (quasi-RCT, Canada, +) assessed the effectiveness of eight sessions of a smoking cessation programme compared to using four sessions in 85 participants with severe and persistent mental illness. The study reported no significant differences between quitters and non-quitter from baseline to 12 month for a range of psychiatric symptoms scales (Brief Psychiatric Rating Scale thought differences, Brief Symptom Inventory, Global Assessment of Functioning). The Brief Psychiatric Rating Scale affective distress score decreased significantly over time ($p<0.05$), however this was independent of whether the participants quit or not.

Kisely 2003 (NRCT, Australia, -) assessed the effectiveness of a high intensity behavioural group therapy in 38 outpatients with a range of psychiatric disorders. The study reported no significant effect was seen of high intensity behavioural group therapy on psychiatric symptoms, as assessed using the General Health Questionnaire ($p=0.238$).

Morris 2011 (RCT, USA, +) assessed the effectiveness of a tobacco cessation group therapy programme in addition to a quit-line service in 123 outpatients with psychiatric diagnoses. For each treatment group from baseline to 6 months follow-up, significant reduction were seen for psychiatric symptoms scales (Hamilton Depression Scale, $p<0.01$; Brief Psychiatric Rating Scale, $p<0.01$); significantly lower levels were seen for nicotine dependence (FTND, $p<0.0001$); and significant improvements were seen for quality of life (Short Form health survey, $p<0.0001$). However, no significant differences were detected in the change scores between the treatment groups for the above scales (all $p>0.05$).

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

George 2000 (quasi-RCT, USA, +) assessed the effectiveness of a specialised schizophrenia group therapy programme compared to standard therapy programme in 45 participants with schizophrenia or schizoaffective disorders. No significant differences were seen in psychiatric symptoms; however, the psychological symptoms of nicotine abstinence (assessed using the psychological subscale of the

Shiffman-Jarvik Nicotine Withdrawal Scale) significantly increased in those who were abstinent compared to non-abstinent participants at week 4 ($p<0.01$).

Williams 2010 (RCT, USA, +) assessed the effectiveness of a high intensity behavioural counselling programme compared to a medium intensity programme in 100 outpatients with schizophrenia or schizoaffective disorders. No significant differences were seen for changes from baseline to week 12 post target quit date for positive symptoms (assessed using PANSS, $p=0.90$), negative symptoms (assessed using PANSS, $p=0.49$), or for depression (Becks Depression Inventory, $p=0.41$). Additionally, no significant differences in these scales were seen between those who had and had not achieved abstinence. The study reported no evidence of worsening of psychosis or mood symptoms in participants who took part in the trial.

POST-TRAUMATIC STRESS DISORDER

McFall 2005 (RCT, USA, +) assessed the effectiveness of integrated care in 66 outpatients under treatment for PTSD. The study reported no significant changes in mental health symptoms from baseline to 6 or 9 months follow-up in a sample as a whole (all $p>0.05$).

McFall 2010 (RCT, USA, ++) assessed the effectiveness of integrated care in 943 outpatients with PTSD. Over the 18 months trial, no significant difference was seen between the integrated care and usual standard care groups for psychiatric symptoms (PTSD Checklist and Patient Health Questionnaire); however, the PTSD severity was noted to improve in both of the treatment groups by approximately 10% (Clinician Administered PTSD Scale).

EVIDENCE STATEMENTS

ES24.1 There is moderate evidence from three trials in populations with mental health disorders (**Kisely 2003 [NRCT, Australia, -]; Currie 2008 [quasi-RCT, Canada, +]; Morris 2011 [RCT, USA, +]**) to suggest high intensity behavioural therapy programmes did not worsen mental health outcomes compared to standard behavioural therapy programmes on psychiatric symptoms.

ES24.2 There is moderate evidence from two trials focusing on populations with schizophrenia (**George 2000 [quasi-RCT, USA, +]; Williams 2010 [RCT, USA, +]**) to suggest high intensity behavioural therapy programmes did not worsen mental health outcomes compared to standard behavioural therapy programmes on psychiatric symptoms.

ES24.3 There is moderate evidence from two trials focusing on populations with PTSD (**McFall 2005 [RCT, USA, +]; McFall 2010 [RCT, USA, ++]**) to suggest high intensity behavioural therapy programmes did not worsen mental health outcomes compared to standard behavioural therapy programmes on psychiatric symptoms.

There is no reason to assume that unintended consequences related to the use of high intensity behavioural therapy programmes are not applicable to the UK setting.

BUPROPION

Nine of the trials included in the review assessed the impact of unintended consequences of bupropion.

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

Akbarpour 2010 (RCT, Iran, +) assessed the effectiveness of bupropion (300mg) in 32 male in-patients diagnosed with schizophrenia. Bupropion was significantly associated with enhancement of cognitive function at 12 weeks compared to placebo (p=0.014).

Evins 2001 (RCT, USA, +) assessed the effectiveness of bupropion (150mg) in 18 outpatients diagnosed with schizophrenia. Significant decreases in psychiatric symptoms were seen between the bupropion and placebo groups from baseline to week 12 (Brief Psychiatric Rating Scale, p=0.03) and from week 14-24 (p=0.02). Detailed analysis revealed the differences were primarily related to significant differences in the subscales assessing positive symptoms of psychosis (hallucinations, delusions, and formal thought disorder) and depressive symptoms; however, no significant differences were seen for negative symptoms (baseline to week 12, p=0.17; week 14-24, p=0.08). Depression scores were significantly different between the treatment groups from baseline to week 12 (Hamilton Rating Scale for Depression, p<0.01), but no significant difference was seen from week 14-24 (p=0.06). No differences were seen at the end of week 12 or week 24 for extrapyramidal symptoms (Simpson-Angus Scale) or akathisia (restless leg syndrome assessed using the Hillside Akathisia Scale). Significant reductions in weight were seen in favour of the bupropion group compared to placebo (p=0.02) from baseline to week 12; however no significant difference remained by the end of week 24.

Evins 2005 (RCT, USA, ++) assessed the effectiveness of bupropion (300mg) in 57 outpatients diagnosed with schizophrenia or schizoaffective disorder. A significant difference in the reduction from baseline to week 12 between the bupropion and placebo groups was seen for the cognitive subscale of the PANSS (p=0.029); however, no other significant reductions between the treatment groups were seen for other psychopathology outcomes or their subscales (Scale for Assessment of Negative Symptoms, Hamilton Depression Rating Scale, Hamilton Anxiety Scale, total score for PANSS or its other subscales). No significant reductions were seen in the bupropion group from baseline to week 12 for the psychopathology outcomes or their subscales. No significant differences were seen from baseline to week 12 for within or between treatment group differences (Wisconsin Smoking Withdrawal Scale).

Evins 2007 (RCT, USA, ++) assessed the effectiveness of bupropion (300mg) in 51 outpatients diagnosed with schizophrenia. The study reported no significant differences in psychopathological outcomes relating to negative symptoms (Scale for Assessment of Negative Symptoms), positive or negative symptoms (PANSS), anxiety (State Trait Anxiety Scale), or abnormal involuntary movements (Abnormal Involuntary Movements Scale).

Fatemi 2005 (RCT, USA, –) assessed the effectiveness of bupropion (dose not stated) for smoking reduction in 10 outpatients with schizophrenia or schizoaffective disorders. The study reported there were non-significant decreases in both positive and negative symptoms during the active and placebo phases of the trial as compared to baseline measurements (assessed using the PANSS).

George 2002 (RCT, USA, ++) assessed the effectiveness of bupropion (300mg) in 32 outpatients with schizophrenia or schizoaffective disorders. No significant differences were seen between the groups on positive symptoms of schizophrenia (PANSS); however, there was a reduction in the negative symptoms ($p<0.05$). No significant effects were seen though for craving (Tiffany Questionnaire for Smoking Urges), depression (BDI; $p=0.27$), dyskinetic (Abnormal Involuntary Movement Scale), or extrapyramidal symptoms (Webster Extrapyramidal Scale).

Hertzberg 2001 (RCT, USA, +) assessed the effectiveness of bupropion (300mg) in 15 male combat veteran outpatients with PTSD. No significant changes were seen from baseline to 12 weeks in the bupropion treatment group for a range of self-reported symptoms scales: Davidson Trauma Scale, Pittsburgh Sleep Quality Index, Hamilton Rating Scale for Depression, Clinician Global Impressions Scale, and Hughes Withdrawal Symptoms Checklist. However, a significant difference was seen for the Questionnaire on Smoking Urges scale suggesting bupropion had decreased the urge to smoke ($p<0.0001$).

Weiner 2011b (RCT, USA, ++) assessed the effectiveness of bupropion (300mg) in 46 outpatients diagnosed with schizophrenia or schizoaffective disorders. No significant differences were seen between the bupropion and placebo groups for positive symptoms items of the Brief Psychiatric Rating Scale ($p=0.29$), anxiety/depression items of the Brief Psychiatric Rating Scale ($p=0.64$), or negative symptoms (Scale for the Assessment of Negative Symptoms, $p=0.30$). Additionally, no significant effect was seen on the effect of bupropion on impairment of cognitive function compared with placebo at week 14 (battery of neuropsychological tests were used; $p=0.34$).

BIPOLAR DISORDER

Weinberger 2008 (RCT, USA, –) assessed the effectiveness of bupropion (300mg) in 5 outpatients with a bipolar disorder. No significant mood changes were noted in the participants receiving bupropion (Young Mania Rating Scale, BDI and Hamilton Depression Rating Scale).

EVIDENCE STATEMENTS

ES25.1 There is moderate evidence from eight trials (**Hertzberg 2001 [RCT, USA, +]; George 2002 [RCT, USA, ++]; Arkbapour 2010 [RCT, Iran, +]; Weiner 2011b [RCT, USA, ++]; Evins 2007 [RCT, USA, ++]; Evins 2005 [RCT, USA, ++]; Evins 2001 [RCT, USA, +]; Fatemi 2005 [RCT, USA, -]**) to suggest bupropion (predominately given at 300mg/day) did not worsen mental health outcomes in participants with schizophrenia or schizoaffective disorders.

ES25.2 There is moderate evidence from one trial (**George 2002 [RCT, USA, ++]**) to suggest that whilst bupropion (300mg/day) resulted in no significant difference in positive symptoms of schizophrenia, there was a significant reduction in negative symptoms of schizophrenia.

ES25.3 There is weak evidence from one trial (**Evins 2001 [RCT, USA, +]**) to suggest bupropion (150mg/day) significantly reduces weight in the short term in 18 outpatients diagnosed with schizophrenia.

ES25.4 There is very weak evidence from one trial (**Weinberger 2008 [RCT, USA, -]**) to suggest bupropion (300mg/day) has no detrimental effect on mood changes in 5 outpatients with bipolar disorder.

Unintended consequences related to the use of bupropion are likely to be applicable to the UK setting, as there are no reasons to assume otherwise.

CLOZAPINE

Two trials assessed the impact of unintended consequences of clozapine.

SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDERS

McEvoy 1995 (RCT, USA, –) assessed the effectiveness of different plasma levels of clozapine in 12 chronically hospitalised in-patients with schizophrenia. The medium (200-300ng/ml) and higher (250-450ng/ml) range groups were associated with significantly greater improvements in psychiatric symptoms compared to the lower range group (50-150ng/ml) (Brief Psychiatric Scale, p=0.02; Clinical Global Impressions severity items, p=0.005).

McEvoy 1999 (RCT, USA, +) assessed the effectiveness of different plasma levels of clozapine in 55 smoking and 15 non-smoking in-patients with schizophrenia. Psychiatric symptoms in the 70 participants were significantly more likely to be reduced in the higher dose group (200-450ng/ml, combination of medium and high plasma level groups) than compared to the low plasma level group (50-150ng/ml) (Brief Psychiatric Rating Scale, p=0.003).

EVIDENCE STATEMENT

ES26.1 There is weak evidence from two trials (**McEvoy 1995 [RCT, USA, -]; McEvoy 1999 [RCT, USA, +]**) to support the assumption that moderate to high plasma levels (200-450ng/ml) of clozapine are significantly more likely to reduce psychiatric symptoms and severity of symptoms in schizophrenia than lower plasma levels (50-150ng/ml).

Unintended consequences as a result of using clozapine are likely to be applicable to the UK setting, as there is no reason to assume that this would not be the case.

NICOTINE REPLACEMENT THERAPY

Two studies included in the review assessed the impact of unintended consequences of NRT.

SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDERS

Dalack 1999 (NRCT, USA, –) assessed the effectiveness of NRT patch (22mg) in 10 in-patients diagnosed with schizophrenia or schizoaffective disorders. No significant differences in psychiatric symptoms or antipsychotic-induced Parkinsonism were noted between the two treatment conditions (Brief Psychiatric Rating Scale, Scale for Assessment of Negative Symptoms, Hamilton Depression Scale, Simpson-Angus Scale); however, abnormal involuntary movements increased with the NRT patch plus smoking, where 6 of the 10 participants had an increase (Abnormal Involuntary Movements Scale, $p<0.05$) .

DEPRESSIVE DISORDERS

Hill 2007 (NRCT, USA, –) assessed the effectiveness of NRT patch (14mg) in 9 participants with major depressive disorders. No significant differences were seen between the treatment groups for depression (BDI; p=0.47) or for withdrawal (Minnesota Nicotine Withdrawal Scale, MNWS; p=0.23).

EVIDENCE STATEMENT

ES27.1 There is very weak evidence from one trial (**Dalack 1999 [NRCT, USA, –]**) to suggest NRT patches (22mg/day) had no detrimental effect on psychiatric symptoms in 10 in-patients with schizophrenia.

ES27.2 There is very weak evidence from one trial (**Dalack 1999 [NRCT, USA, -]**) to suggest NRT patches (22mg/day) increased abnormal involuntary movements in those who used the patch whilst still smoking in 10 in-patients with schizophrenia.

ES27.3 There is very weak evidence from one trial (**Hill 2007 [NRCT, USA, -]**) to suggest NRT patches (14mg/day) had no detrimental effect on psychiatric symptoms in 9 participants with major depression.

Unintended consequences related to the use of NRT are applicable to the UK setting as there is no reason to assume that this would not be the case.

VARENICLINE

All four of the trials included in the review assessed the impact on intended consequences of varenicline.

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

Dutra 2012 (UBA, USA, -) assessed the effectiveness of varenicline (2mg) in 102 outpatients diagnosed with schizophrenia or schizoaffective disorders. No significant change from baseline to 12 weeks was seen in the total scores or subscales of the Scale for the Assessment of Negative Symptoms (SANS, p>0.05).

Panchas 2012 (UBA, USA, -) assessed the effectiveness of varenicline (2mg) in 112 outpatients diagnosed with schizophrenia or schizoaffective disorders. Significant improvements from baseline to week 12 or early termination was seen for psychosis (measured using the Brief Psychiatric Rating Scale, BPRS).

Smith 1999 (UBA, USA, –) assessed the effectiveness of varenicline (2mg) in 14 male in-patients and outpatients diagnosed with schizophrenia or schizoaffective disorders. No significant increases were seen for positive symptoms (PANSS positive symptoms, p=0.08), negative symptoms (PANSS negative symptoms, p=0.64), or depression (PANSS depression, p=0.70), or for the overall PANSS score (p=0.69). Suicide ideation or clinically significant depression remained absent during the trial. No significant effect was seen on cognitive function when assessed using the total score for the Repeatable Battery for Assessment of Neuropsychological Status (p=0.67); however significant increases were seen for some components of the battery relating to list learning (p=0.005), language index (p=0.003), and list recall (p=0.03); and significant decreases in visual spatial construction (p=0.03).

Weiner 2011a (RCT, USA, +) assessed the effectiveness of varenicline (2mg) in 9 outpatients with schizophrenia or schizoaffective disorders. No significant difference was seen on positive psychiatric symptoms (Brief Psychiatric Rating Scale, p=0.29) or anxiety/depression scores (Brief Psychiatric Rating Scale, p=0.99) between the varenicline and placebo groups. Suicide ideation remained absent during the trial, and the study reported no significant exacerbations of psychotic, depressive or other psychiatric symptoms in any participants.

EVIDENCE STATEMENTS

ES28.1 There is weak evidence from four trials (**Dutra 2012 [UBA, USA, -]; Panchas 2012 [UBA, USA, -]; Smith 1999 [UBA, USA, -]; Weiner 2011a [RCT, USA, +]**) to suggest varenicline (2mg/day) had no significant detrimental effect on psychiatric symptoms, cognitive function, or suicide ideation in predominately outpatients with schizophrenia.

Unintended consequences from using varenicline are likely to be applicable to the UK setting as there is no reason to assume that this would not be the case.

COMBINATION OF NICOTINE REPLACEMENT THERAPY AND BUPROPION

One trial included in the review assessed the impact of unintended consequence of the combination treatment of NRT and bupropion.

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

George 2008 (RCT, USA, ++) assessed the effectiveness of the combination of bupropion (300mg) and NRT patches (21mg) in 59 outpatients with schizophrenia or schizoaffective disorders. No significant differences were noted relating to positive or negative symptoms of schizophrenia assessed using the PANSS, or depression as assessed using the BDI.

EVIDENCE STATEMENT

ES29.1 There is moderate evidence from trial (**George 2008 [RCT, USA, ++]**) to suggest the combination of bupropion (300mg/day) and NRT patches (21mg/day) had no significant effect on psychiatric symptoms in 59 outpatients with schizophrenia.

Unintended consequences from using the combination of bupropion and NRT are likely to be applicable to the UK setting as there is no reason why this would not be the case.

COMBINATION OF HIGH INTENSITY BEHAVIOURAL THERAPY WITH BUPROPION

One study included in the review assessed the impact of unintended consequences of the combination of high intensity behavioural therapy with bupropion.

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

Weiner 2001 (UBA, USA, –) assessed the effectiveness of high intensity behavioural therapy with bupropion (300mg) for smoking reduction in 9 outpatients with schizophrenia or schizoaffective disorders. The study found no significant changes from baseline to week 14 in positive symptoms of scores (mean, 10.6 versus 10.6), anxiety scores (mean, 2.6 versus 1.9), or depression scores (mean, 1.6 versus 1.8) (assessed using the Brief Psychiatric Rating Scale); negative symptom scores (Scale for the Assessment of Negative Symptoms, mean, 29.4 versus 24.1; p=0.12); or changes on any cognitive measure (p>0.05). However, the study did demonstrate a significant reduction in alogia (inability to speak) factor scores from baseline to week 14 (Scale for the Assessment of Negative Symptoms, mean, 3.0 versus 1.1; p<0.05).

EVIDENCE STATEMENT

ES30.1 There is very weak evidence (**Weiner 2001 [UBA, USA, -]**) to suggest the combination of high intensity behavioural therapy with bupropion (300mg/day) for smoking reduction has no detrimental effect depression, anxiety, or psychiatric symptoms in 9 outpatients with schizophrenia; however, some evidence of an improvement was seen for alogia.

Unintended consequences from using the combination of high intensity behavioural therapy with bupropion are likely to be applicable to the UK setting as there is no reason why this would not be the case.

HIGH INTENSITY BEHAVIOURAL THERAPY AND NICOTINE REPLACEMENT THERAPY

Three trials included in the review assessed the impact of unintended consequences of high intensity behavioural therapy in addition to nicotine replacement therapy.

MENTAL HEALTH DISORDERS

Baker 2009 (NRCT, Australia, –) assessed the effectiveness of CBT and MI with NRT (42mg) patches in 48 outpatients with a non-acute psychotic disorder. No significant changes were seen from baseline to post-treatment assessment for quality of life (Short Form survey, mental components: p=0.13; physical health components: p=0.89), depression (BDI, p=0.96), or psychotic symptoms (Brief Psychiatric Rating Scale, p=0.51).

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

Baker 2006 (RCT, Australia, +) assessed the effectiveness of a CBT and MI with NRT patches (21mg) in 298 in-patients and outpatients with a diagnosis of schizophrenia or schizoaffective disorders. No significant differences were seen between the treatment groups for overall psychopathology (Brief Psychiatric Scale), quality of life (physical components of Short Form survey), anxiety (State-Trait Anxiety Inventory), or depression (BDI). However within the groups, significant reductions were seen for anxiety from baseline to 6 months ($p<0.001$), depression from baseline to all three outcome timings (3 months, $p<0.001$; 6 months, $p<0.001$; 12 months, $p<0.001$), and the mental components of the quality of life scale (Short Form survey) from baseline to all three outcome timings (3 months, $p<0.001$; 6 months, $p<0.01$; 12 months, $p<0.01$).

MAJOR DEPRESSION

Barnett 2008 (RCT, USA, +) assessed the effectiveness of a high intensity behavioural programme with NRT (dose not given) in 322 outpatients with uni-polar depression. No significant difference in depression was seen between the stepped care and brief contact groups (assessed using the BDI).

EVIDENCE STATEMENT

ES31.1 There is very weak evidence from one trial (**Baker 2009 [NRCT, Australia, –]**) to suggest the combination of high intensity behavioural therapy with NRT patches (42mg/day) had no significant effect on psychiatric symptoms or quality of life in 48 outpatients with a non-acute psychotic disorder.

ES31.2 There is weak evidence from one trial (**Baker 2006 [RCT, Australia, +]**) to suggest the combination of high intensity behavioural therapy with NRT (21mg/day) had no significant effect on psychiatric symptoms, quality of life, depression, or anxiety in 298 in-patients an outpatients with schizophrenia.

ES31.3 There is weak evidence from one trial (**Barnett 2008 [RCT, USA, +]**) to suggest the combination of high intensity behavioural therapy with NRT (dose not stated) had no significant effect on depressive symptoms in 322 outpatients with major depression.

Unintended consequences as a result of using the combination of high intensity behavioural therapy with NRT are applicable to the UK setting as there is no reason why this would not be the case.

COMBINATION TREATMENT OF CONTINGENCY PAYMENTS AND BUPROPION

One trial included in the review assessed the impact of unintended consequences of the combination of contingency payments and bupropion.

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

Tidey 2011 (RCT, USA, ++) assessed the effectiveness of contingency payment with bupropion (300mg) in 57 outpatients with a diagnosis of schizophrenia or schizoaffective disorders. No significant differences were detected between the treatment groups for psychopathology related outcomes (PANSS, Motor Examination section of the Unified Parkinson's Disease Rating Scale, Abnormal Involuntary Movements Scale, all $p<0.05$); however, across the treatment groups all of these outcomes significantly reduced from baseline (week 1) (Questionnaire on Smoking Urges, $p<0.001$; PANSS, $p<0.001$; Motor Examination section of the Unified Parkinson's Disease Rating Scale, $p<0.001$; Abnormal Involuntary Movement Scale, $p<0.001$).

EVIDENCE STATEMENT

ES32.1 There is moderate evidence from one trial (**Tidey 2011 [RCT, USA, ++]**) to suggest contingency payments given in addition to bupropion (300mg/day) does not have a detrimental effect on psychiatric symptoms in 57 outpatients with schizophrenia.

Unintended consequences as a result of using the combination of contingency payments with bupropion are likely to be applicable to the UK setting as there is no reason why this would not be the case.

COMBINATION OF CONTINGENCY PAYMENTS AND NICOTINE REPLACEMENT THERAPY

One trial included in the review assessed the impact of unintended consequences of the combination treatment of contingency payments with NRT.

SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDERS

Gallagher 2007 (RCT, USA, –) assessed the effectiveness of contingency payments with NRT (21mg) in 180 outpatients diagnosed with schizophrenia or schizoaffective disorders. No significant changes from baseline to week 20 or week 36 were seen in self-reported psychiatric symptoms (Brief Symptoms Inventory).

EVIDENCE STATEMENT

ES33.1 There is very weak evidence from one trial of 180 outpatients with schizophrenia or schizoaffective disorders (**Gallagher 2007 [RCT, USA, -]**) to suggest contingency payments given in addition to NRT (21mg/day) does not have detrimental effects on psychiatric symptoms in the short term and medium term.

Unintended consequences as a result of using the combination of contingency payments with NRT are likely to be applicable to the UK setting as there is no reason why this would not be the case.

QUESTION 2. HOW EFFECTIVE ARE CURRENT STRATEGIES/APPROACHES USED BY SECONDARY CARE MENTAL HEALTH SERVICES FOR IDENTIFYING AND REFERRING PEOPLE FROM THE POPULATION OF INTEREST TO STOP SMOKING OR HOSPITAL BASED STOP SMOKING SERVICES?

No studies were identified which assessed the effectiveness of current strategies or approaches used by secondary care mental health services for identifying and referring people from the population of interest to stop smoking or hospital based stop smoking services. However, information relating to the barriers and facilitators of current strategies and approaches used are presented in Review 5.

EVIDENCE STATEMENT

ES34.1 No studies were identified which assessed the effectiveness of current strategies or approaches used by secondary care mental health services for identifying and referring people from the population of interest to stop smoking or hospital based stop smoking services.

QUESTION 3. HOW EFFECTIVE ARE CURRENT STRATEGIES/APPROACHES USED BY SECONDARY CARE MENTAL HEALTH SERVICES FOR IDENTIFYING AND PROVIDING PEOPLE FROM THE POPULATION OF INTEREST WITH SMOKING CESSATION INFORMATION, ADVICE AND SUPPORT?

No studies were identified which assessed the effectiveness of current strategies or approaches used by secondary care mental health populations for identifying and providing people from the population of interest with smoking cessation information, advice and support. However, information relating to the barriers and facilitators of current strategies and approaches used are presented in Review 5.

EVIDENCE STATEMENT

ES35.1 No studies were identified which assessed the effectiveness of current strategies or approaches used by secondary care mental health populations for identifying and providing people from the population of interest with smoking cessation information, advice and support.

QUESTION 4. WHICH STRATEGIES/APPROACHES ARE EFFECTIVE IN ENCOURAGING MENTAL HEALTH CARE PROFESSIONALS TO RECORD SMOKING STATUS AND REFER POPULATIONS OF INTEREST TO STOP SMOKING SERVICES?

No studies were identified which assessed the effectiveness of strategies for encouraging mental health professional to record smoking status, or refer populations of interest to stop smoking services. However, one primary study was identified which assessed the effectiveness of an intervention for encouraging the participants with mental health illness to refer to a stop smoking service. The study was summarised in detail in the evidence table in Appendix 7. The findings from this study are presented below. The internal validity quality score for the study is presented in parentheses following the citation.

BEHAVIOURAL INTERVENTIONS

HIGH INTENSITY BEHAVIOURAL THERAPY INTERVENTIONS

Steinberg 2004 (RCT, USA, ++) A RCT was performed to assess the effectiveness of high intensity behavioural therapy programme for motivating 78 outpatient smokers with schizophrenia or schizoaffective disorders for referral to stop smoking service. Participants were randomised to one of three groups, and each received only one therapy session. The first treatment group used a high

intensity behavioural programme based on motivation interviewing (duration 40 minutes) and included personalized feedback. The second treatment group used psycho-educational intervention where participants discussed the general benefits of quitting and harmful effects of smoking (duration 40 minutes). The third treatment group used a brief intervention (duration 5 minutes). At the end of the sessions, all participants were given advice concerning quitting smoking and were referred to a specialised stop smoking service.

Referring to stop smoking services

The study demonstrated a higher proportion of participants sought treatment at the stop smoking service in the motivational interviewing group (25.8%) compared to the psycho-educational (0%) and brief intervention (0%) groups at one week post-therapy session. Similar effects were reported at one month post therapy session (MI, 32.3% versus psycho-educational, 11.8% versus brief intervention, 0%).

EVIDENCE STATEMENTS

ES36.1 No studies were identified which assessed the effectiveness of current strategies or approaches used by secondary care mental health populations for recording smoking status in the population of interest.

ES36.2 No studies were identified which assessed the effectiveness of current strategies or approaches used by secondary care mental health populations for referring populations of interest to stop smoking services.

ES36.3 There is moderate evidence from one trial of 78 outpatients with schizophrenia (**Steinberg 2004 [RCT, USA, ++]**) to suggest that a single session of motivational interviewing resulted in a higher proportion of participants seeking referral for a stop smoking service compared to psycho-educational or brief intervention.

The evidence from the individual study of high intensity behavioural therapy as an intervention to increase referral to a stop smoking service is directly applicable to the UK as the study was based on an outpatient population with mental health disorders, and the intervention is feasible in the UK setting as it is currently used for smoking cessation in the general population. The study was conducted in the USA.

Table 16 Summary evidence table for high intensity behavioural therapy for referral to stop smoking service

Study details	Location and setting	Description of population	Outline of study	Internal validity score
Steinberg 2004 RCT, n=78	**Location:** USA **Setting:** Outpatient	At least 10 cigarette per day, diagnosis of schizophrenia or schizoaffective disorder **Motivation:** Didn't require participants to quit smoking	**Intervention:** Motivational interviewing group – personalised feedback based on assessment interview, duration approximately 40 minutes and concluded with advice to quit smoking and with a referral for treatment to a specialised tobacco dependence treatment programme **Control:** Psycho-educational intervention – engaged in brief psycho-educational discussion on general benefits of quitting and the deleterious health effects of smoking based on standard protocol, predominately didactic but encouraged discussion (40 minute intervention). Concluded intervention with advice to quit and referral for treatment **Outcome:** Referral to stop smoking service	++ **Limitations:** Self-selected participants, lead researcher delivered interventions, participants charts relied on for diagnoses, unknown quit rate, minimal intervention had much less contact so comparisons with this could be related to contact rather than content, but the other treatment groups were comparable

DISCUSSION

This review of smoking cessation in secondary mental health services comprises of a large body of evidence. Fifty-nine studies were identified, of which 10 were based on systematic or critical review methodology and the remaining 49 were primary evidence. The majority of the studies assessed the effectiveness of interventions in schizophrenia, with only a few studies assessing outcomes in different mental health populations. Most interventions assessed included behavioural therapies, bupropion, NRT, varenicline. The majority of studies were conducted in the United States, with few studies from other countries, and no studies were identified from the UK. The methodological quality of the studies was very variable, with few studies being awarded the highest quality for both internal and external validity. The majority of studies presented smoking abstinence using bio-verification of either expired CO or cotinine levels.

Overall, the evidence from the review suggested:

BEHAVIOURAL THERAPY (WITH NO PHARMACOTHERAPY)

Very few well conducted high quality studies have been performed to assess the effectiveness of high intensity behavioural therapy for smoking cessation or reduction. However, the evidence to date suggests high intensity behavioural therapy may be effective in populations with specific mental health disorders.

- The effectiveness of high intensity behavioural therapy in people with psychiatric disorders is mixed and mostly based on weak evidence, where an effect was seen in the short term in adults for cessation and smoking reduction, but no effect on cessation was seen in the long term in adolescents. However, there was moderate evidence that integrated tailored behavioural therapy was more effective for smoking cessation in PTSD in the short and long term, than usual standard of care (referral to a specialised smoking cessation clinic)
- There was moderate evidence to suggest high intensity behavioural therapy did not appear to be more effective for smoking cessation than lower intensity behavioural therapy in the short term in schizophrenia on cessation; however, it should be noted that in one of the studies the intensity of the behavioural therapy in the control group was relatively high
- There was moderate evidence to suggest low intensity behavioural therapy was not effective for smoking cessation or reduction in schizophrenia; however, there was very weak evidence to suggest it may be effective for smoking reduction in other psychiatric populations
- There was moderate evidence to suggest motivational interviewing may be effective in increasing the number of people with mental health disorders to seek referral for a stop smoking service compared to psycho-educational or brief intervention.

BUPROPION

Several well conducted high quality studies have been performed to assess the effectiveness of bupropion for smoking cessation or reduction. The evidence to date suggests bupropion is effective for smoking cessation in the short term in populations with schizophrenia.

- There was strong evidence that bupropion was effective for increasing smoking cessation in the short term in schizophrenia, but the effect in the medium and long term is unclear
- There was moderate evidence to suggest bupropion was effective for smoking reduction in the short term in schizophrenia
- There was very weak evidence to suggest bupropion did not appear to be effective for smoking cessation in PTSD or bipolar

NICOTINE REPLACEMENT THERAPY (NRT)

Very few well conducted high quality studies have been performed to assess the effectiveness of NRT for smoking cessation or reduction. The evidence to date is mixed regarding whether NRT is effective in populations with mental health disorders.

- There was weak evidence to suggest high dose NRT may be more effective than standard dose NRT for cessation in schizophrenia
- There was mixed very weak evidence to suggest NRT regarding the effectiveness of NRT for smoking reduction or cessation in major depression or schizophrenia in the short term

VARENICLINE

No well conducted high quality studies have been performed to assess the effectiveness of varenicline for smoking cessation or reduction. The evidence to date suggests varenicline may have some effectiveness for reducing smoking.

- There was weak evidence to suggest varenicline may reduce smoking consumption, but was not effective for abstinence, in schizophrenia

OTHER PHARMACOTHERAPIES

Very few well conducted moderate to high quality studies have been performed to assess the effectiveness of other pharmacotherapies for smoking cessation or reduction. The evidence to date suggests clozapine (an atypical [new generation] antipsychotic medication) may be effective for reducing smoking.

- There was moderate evidence to suggest higher doses of clozapine (350-600mg/day) may be effective for smoking reduction, but no effect was seen for smoking cessation, in schizophrenia.
- There was very weak evidence to suggest fluoxetine did not appear to be effective for smoking reduction in major depression
- There was very weak evidence to suggest galantamine did not appear to be effective for smoking reduction in schizophrenia
- There was moderate evidence to suggest naltrexone was not effective for smoking cessation or reduction in consumption in schizophrenia

COMBINATIONS OF INTERVENTIONS

Very few well conducted high quality studies have been performed to assess the effectiveness of combinations of interventions as compared to control. The evidence to date suggests the combination of bupropion with NRT may be effective for smoking cessation.

- There was very weak evidence to suggest the combination of bupropion with NRT may be effective in reducing smoking consumption in psychiatric populations
- There was moderate evidence to suggest the combination of bupropion with NRT was effective for smoking cessation in the short term, but not in the long term, in schizophrenia
- There was very weak evidence to suggest the combination of high intensity behavioural therapy with bupropion may reduce smoking consumption in schizophrenia
- There was weak evidence to suggest the combination of high intensity behavioural therapy with NRT may be effective for reducing smoking consumption, but had no effect on cessation, in non-acute psychotic disorders or depression

CONTINGENCY PAYMENTS (WITH OR WITHOUT PHARMACOTHERAPIES)

Very few well conducted high quality studies have been performed to assess the effectiveness of contingency payment with or without pharmacotherapies for smoking cessation or reduction. The evidence to date suggests the combination of contingency payments with bupropion was effect for reducing smoking in specific mental health populations.

- There was weak evidence to suggest contingency payments may be effective for reducing smoking consumption in schizophrenia
- There was moderate evidence to suggest contingency payments with bupropion was effective on reducing smoking in schizophrenia
- There was very weak evidence to suggest contingency payments with NRT patches may be effective for a reduction in smoking consumption and smoking abstinence in schizophrenia

EFFECTIVENESS OF INTERVENTION BY TYPE OF ANTI-PSYCHOTIC MEDICATION

There were several well conducted high quality studies that have been performed to assess the difference in effectiveness of interventions for smoking cessation by the type of anti-psychotic medication used. The evidence to date is mixed regarding whether the effectiveness differs between using typical and atypical antipsychotic medication.

- There was mixed moderate evidence regarding the difference in effectiveness of high intensity behavioural therapy or bupropion for smoking cessation by the type of anti-psychotic medication used in schizophrenia.

No studies were identified which assessed:

- The effectiveness of interventions for temporary abstinence in people with mental health illness.
- The effectiveness of current strategies or approaches used by secondary care mental health services for identifying and referring people from the population of interest to stop smoking or hospital based stop smoking services.
- The effectiveness of current strategies or approaches used by secondary care mental health populations for identifying and providing people from the population of interest with smoking cessation information, advice and support.

- The effectiveness of current strategies or approaches used by secondary care mental health populations for referring populations of interest to stop smoking services.

This review was conducted to a high methodological quality by performing a comprehensive and systematic search strategy which was based on searching multiple electronic databases, websites, and reference screening. Additionally, double screening of titles, abstracts and full texts were performed independently, and high agreements rates were seen for screening, data extraction and quality assessments. However, the review is not without limitations. The majority of the studies included in the review were conducted in the USA, with no studies being identified from the UK; therefore, the applicability of the evidence and generalisability from these other settings to the UK needs to be considered. However, while idiosyncrasies in the structure of mental health service provision in different countries need to be acknowledged, there is no reason to believe that interventions which are effective in one country would not be in another, assuming similar patient characteristics Since none of the studies included in this review was conducted in high secure (forensic) service settings, the findings from this review are only generalisable to inpatient settings of low to medium (and often mixed open/secure) security; however, it would be of interest in the future for studies to assess the effectiveness of interventions, in particular relating to temporary abstinence, in high security inpatient settings. Most of the studies included in this review included patients whose conditions was assessed as stable. Therefore, it is unclear whether the interventions would be of similar effectiveness for patients in the acute phase of illness. In the future, studies should consider assessing the effectiveness of smoking cessation and temporary abstinence interventions in this group of patients (for example on assessment wards and intensive care units); however, this patient group would be very challenging to study due to complex practical and ethical implications of conducting research in a group of acutely ill patients. Additionally when conducting future studies, researchers need to consider the attitudes of staff and the historic culture of smoking in mental health settings, since these can often undermine change in these settings (please refer to Review 5: Barriers and Facilitators for smoking cessation interventions in mental health). The review is also subject to methodological limitations primarily relating to tight time constraints, where authors of the original studies could not be contacted to provide further information where necessary. Additionally, few meta-analyses could be performed due to the differences in interventions, study design, mental health populations, and outcome measures; therefore the evidence from this review is based predominately on a narrative summary, with the studies providing evidence that was inconclusive regarding the effectiveness of several interventions. However, this review highlights the urgent need for further high quality research to be performed in the areas of smoking cessation and reduction, and temporary abstinence in secondary care mental health service settings in the majority of the identified areas, and particularly in the UK.

REFERENCES

1. Kelly, C. and R. McCreadie, *Cigarette smoking and schizophrenia.* Advances in psychiatric treatment, 2000. **6**: p. 327-331.
2. de Leon, J. and F. Diaz, *A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors.* Schizophrenia Research, 2005. **76**: p. 135-157.
3. Williams, J., D. Ziedonis, F. Abanyie, et al., *Increased nicotine and cotinine levels in smokers with schizophrenia and schizoaffective disorder is not a metabolic effect.* Schizophrenia Research, 2005. **79**: p. 323-335.
4. Ziedonis, D., B. Hitsman, J. Beckham, et al., *Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. .* Nicotine and Tobacco Research, 2008. **10**: p. 1691-1715.
5. El-Guebaly, N., J. Cathcart, S. Currie, et al., *Public health and therapeutic aspects of smoking bans in mental health and addiction settings.* Psychiatr Serv, 2002. **53**(12): p. 1617-22.
6. Olivier, D., D. Lubman, and R. Fraser, *Tobacco smoking within psychiatric inpatient settings: biopsychosocial perspective.* Australian and New Zealnd Journal of Psychiatry, 2007. **41**: p. 572-580.
7. McNeill, A., *Smoking and mental health: a review of the literature.* Smokefree London Programme, 2001.
8. Glassman, A.H., *Psychiatry and Cigarettes. .* Arch Gen Psychiatry, 1998. **55**: p. 692-693.
9. Lawn, S. and J. Condon, *Psychiatric nurses' ethical stance on cigarette smoking by patients: determinants and dilemmas in their role in supporting cessation.* International Journal of Mental Health Nursing, 2006. **15**: p. 118.
10. Lawn, S., *Systemic factors that perpetuate smoking among community and institutionalised public mental health service populations.* Australia: Department of social administration and social work, Faculty of Social Sciences, Flinders University, 2001.
11. Ratschen, E., J. Britton, G.A. Doody, et al., *Smoke-free policy in acute mental health wards: avoiding the pitfalls.* Gen Hosp Psychiatry, 2009. **31**(2): p. 131-6.
12. Ratschen, E., J. Britton, G.A. Doody, et al., *Tobacco dependence, treatment and smoke-free policies: a survey of mental health professionals' knowledge and attitudes.* Gen Hosp Psychiatry, 2009. **31**(6): p. 576-82.
13. Siru, R., G.K. Hulse, and R.J. Tait, *Assessing motivation to quit smoking in people with mental illness: a review.* Addiction, 2009. **104**(5): p. 719-33.
14. Williams, J. and J. Foulds, *Successful Tobacco Dependence Treatment in Schizophrenia.* American Journal of Psychiatry, 2007. **164**: p. 222-227.
15. Banham, L. and S. Gilbody, *Smoking cessation in severe mental illness: what works? (Structured abstract).* Addiction, 2010. **105**(7): p. 1176-1189.
16. Stead, L. and T. Lancaster, *Group behaviour therapy programmes for smoking cessation* Cochrane Database of Systematic Reviews, 2005. **Issue 2**: p. John Wiley & Sons , Ltd Chichester, UK DOI : 10 1002 /14651858 CD001007 pub2.
17. Addington, J., *Group treatment for smoking cessation among persons with schizophrenia.* Psychiatric Services (Washington, D.C.), 1998. **49**(7): p. 925-928.
18. Williams, J. and D. Ziedonis, *Addressing tobacco among individuals with a mental illness or an addiction.* Addictive Behaviors, 2004. 29: p. 1067-1083.