Smoking cessation for improving mental health (Protocol)

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Smoking cessation for improving mental health

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To investigate the association between tobacco smoking cessation and subsequent mental health outcomes.
**BACKGROUND**

**Description of the condition**

Smoking is the world's leading cause of preventable illness and death (WHO 2011). One in every two smokers will die of a smoking-related disease, unless they quit (Doll 2004; Pirie 2013). In high-income countries, the prevalence of smoking has decreased markedly from the 1970s; for example, in the UK it has fallen from 46% to approximately 14.9% in 2018 (ONS 2018; West 2019). However, smoking prevalence amongst people with mental illness has declined only slightly and is currently around 32% (Richardson 2019; Szatowski 2015; Taylor 2019). Smokers with mental illness are more heavily addicted, suffer from worse withdrawal (Hitsman 2013; Leventhal 2013; Leventhal 2014; RCP/RC PSYCH 2013), and are less responsive to standard treatments (Hitsman 2013; Taylor 2019), even though they are motivated to quit (Haakkaara 2000; Siru 2009). These inequalities contribute to a reduction in life expectancy of up to 17.5 years compared to the general population (Chang 2011; Chesney 2014).

**Description of the intervention**

Some smokers and healthcare providers believe that smoking can reduce stress and other symptoms related to mental illness, and these beliefs maintain a culture of smoking in mental health settings (Cookson 2014; Sheals 2016). However, our previously published review found a strong association between smoking cessation and improvements in mental health that were equal to or larger than the effect of taking antidepressants (Taylor 2014). We argued that this was likely to be causal, and that smoking cessation can lead to improved mental health.

**How the intervention might work**

Chronic tobacco smoking is associated with neuroadaptations in nicotinic pathways in the brain. Neuroadaptations in these pathways are associated with the occurrence of withdrawal symptoms, such as depressed mood, agitation and anxiety. Withdrawal symptoms are alleviated by smoking and remain alleviated shortly after smoking, but symptoms return when blood levels of nicotine decline at around 20 minutes after smoking (Benowitz 1990; Benowitz 2010; Mansvelder 2002); this is known as the withdrawal cycle and is marked by fluctuations in a smoker's psychological state throughout the day (Benowitz 2010; Parrott 2003). Therefore, smokers and non-smokers alike mistake the ability of tobacco to alleviate tobacco withdrawal for an ability to alleviate mental health-related symptoms. This misunderstanding has negative consequences in treating tobacco addiction in mental health populations, as many healthcare providers believe that by helping their patients to quit smoking, they will be harming their patients' mental health (Cookson 2014; Sheals 2016).

Recent observational studies have used methods that support strong causal inference, to indicate that smoking increases the risk of depression and schizophrenia (Wootton 2018), and that smoking cessation leads to a reduction in the prescription of antidepressants and anxiolytics (Taylor 2019). When inferring causal associations from epidemiological studies, it is important to consider the strength of association, reverse causation, potential confounding, and biological plausibility. To date, there is evidence that our hypothesis that smoking cessation improves mental health meets these considerations.

- Strength of association: the strength of the pooled association in our previous review, exploring the association between smoking cessation and mental health (Taylor 2014), was clinically important - the association between smoking cessation and change in depression and anxiety was equal to or larger than the estimate from trials of antidepressants versus placebo. Fournier 2010 meta-analysed individual-level data from randomised controlled trials (RCTs) (6 RCTs, N = 718) of selective serotonin reuptake inhibitors for "mild" to "severe" depression. The resulting effect estimates ranged from standardised mean difference (SMD) −0.11, 95% confidence interval (CI) - 0.26 to −0.04 to SMD −0.47, 95% CI −0.59 to −0.34 for change in depression. The effect size for smoking cessation was SMD −0.25, 95% CI −0.37 to −0.12, which falls within this range (Taylor 2014). A meta-analysis of 34 RCTs assessed the effect of antidepressants on generalised anxiety disorder (NCCMH 2011), and effect estimates ranged from SMD −0.23, 95% CI −0.32 to −0.14 to SMD −0.50, 95% CI −0.77 to −0.23; this is similar to the effect smoking cessation had on anxiety (SMD −0.37, 95% CI −0.70 to −0.03).

- Reverse causation: one explanation for the association between smoking cessation and improvements in mental health is that improved mental health prompts people to attempt cessation. However, over half of the studies in our previous review were secondary analyses of RCTs (Taylor 2014). In these studies everyone attempted cessation, and therefore the decision to quit was not contingent on change in mental health. Observed changes in mental health were measured after entry into the trials. Subgroup analyses showed no difference between estimates that were derived from RCTs and from population cohorts (in which reverse causation was more likely). Second, a recent study employing mendelian randomisation, one of the strongest available causal methods in epidemiology, also supports this relationship between smoking and mental health by providing evidence that smoking causes mental illnesses, such as depression and schizophrenia (other mental illnesses were not examined) (Wootton 2018). It could be that improved mental health predicts the likelihood of a successful quit attempt or that worsened mental health after cessation predicts relapse. However, in our previous observational analysis of RCT data there was no greater tendency to relapse at 12 months for those whose mental health worsened after cessation compared with those who had no change or an improvement; odds ratio (OR) 1.01, 95% CI 0.97 to 1.05 (Taylor 2015).

- Potential confounding: in our previous review, two studies supplying estimates for the change in three mental health outcomes (i.e. anxiety, depression, and positive affect) provided effect sizes adjusted for confounders (Taylor 2014). The confounders included demographics, tobacco consumption, and/or treatment allocation. Comparison of these adjusted estimates with unadjusted estimates indicated no meaningful change in the results. Another study triangulated evidence for the relative effect of varenicline compared to nicotine replacement therapy on mental health outcomes (i.e. depression, anxiety, antidepressants and anxiolytics) (Taylor 2019). The study used three analytical approaches, allowing for different levels of control for confounding: multivariable regression modelling (little control for confounding), propensity score matched regression modelling (less susceptible to confounding), and instrumental variable analysis (unlikely to be affected by confounding). All three models consistently found...
that varenicline was associated with decreased odds of receiving mental health diagnoses and prescriptions, suggesting that no confounding factors were influencing the results.

- Biological plausibility: the hypothesis that cessation improves mental health is supported by a plausible biological mechanism, related to neuroadaptations in nicotinic pathways in the brain (Benowitz 2010), as previously described. The constant fluctuation in withdrawal-induced psychological symptoms experienced by smokers could worsen mental health over time, and the associated biological effects could increase the risk of mental illness (Parrott 2003; Wootton 2018). It is likely that after breaking the tobacco withdrawal cycle, through quitting smoking, these systems recover (Mamede 2007), in the same way that other systems damaged by tobacco heal after cessation (Doll 2004; Pirie 2013). This is consistent with reports that withdrawal symptoms abate a few weeks after quitting smoking (Hughes 2007).

Why it is important to do this review

There is little convincing evidence that the smoking epidemic amongst people with mental illness is subsiding to the same level as observed in the general population - the gap in prevalence between smokers with and without mental illness is not closing (Richardson 2019; Taylor 2019). Given evidence of therapeutic nihilism amongst healthcare professionals (Sheals 2016), strengthening, communicating and updating the evidence exploring the association between smoking and mental health is critically important to populations with mental illness. It could also encourage people who smoke without mental illness to quit and discourage others from beginning to smoke tobacco.

OBJECTIVES

To investigate the association between tobacco smoking cessation and subsequent mental health outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled before-after studies, including randomised controlled trials (RCTs) analysed by smoking status. We will conduct secondary analysis of RCTs and cohort studies to compare those who quit smoking with continuing smokers, rather than compare the randomised study arms.

Types of participants

Adult (using definitions given in included studies) tobacco smokers who continue or quit smoking; no restrictions by population or comorbid conditions.

Types of interventions

The intervention will be quitting smoking. We will include any definition of smoking cessation, as defined by the included studies (i.e. self-report, bio-validated, point prevalence, continuous). We will prefer more stringent measures, and intention-to-treat over complete case analysis where multiple definitions of quitting are reported.

Types of outcome measures

Self-report or clinician scored measures of mental health. We will include continuous and dichotomous measures of mental health, or mental ill-health.

Primary outcomes

- Change in depression symptoms, at least six weeks follow-up from baseline
- Change in anxiety symptoms, at least six weeks follow-up from baseline
- Change in mixed anxiety and depression, at least six weeks follow-up from baseline

Secondary outcomes

- Change in symptoms of stress, psychological quality of life, and positive affect
- Mental ill-health, including measures of depression, anxiety, stress, psychological quality of life, positive effect, mixed anxiety and depression
- Social impact, including measures of social satisfaction, interpersonal relationships, isolation and loneliness. We carried out patient and public involvement work to identify any outcomes of particular relevance to members of the public, which were not considered in the previous version of this review (Fournier 2010). This work highlighted that people who smoke may be concerned that quitting could disrupt their social networks, and lead to feelings of loneliness. This may be of particular significance to people also experiencing mental ill-health.

Search methods for identification of studies

Electronic searches

We will search Cochrane Central Register of Controlled Trials, MEDLINE, Embase, PsycINFO, and the Cochrane Tobacco Addiction Group’s Specialised Register. The most recent searches of these databases for the previous non-Cochrane version of this review were carried out on 13 April 2012 (Taylor 2014). The inclusion criteria specified in this protocol do not differ from those in the original review, therefore we will include studies included in the previous review and conduct updated searches from 14 April 2012 to present, to identify any new studies. See Appendix 1 for the MEDLINE search strategy.

Searching other resources

We will search the reference lists of eligible studies, and the following trial databases: ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/ICTRP).

Data collection and analysis

Selection of studies

Our aim will be to maximise sensitivity by including studies in initial screens even if data directly relevant to our question are not presented in the abstract. The titles and abstracts of eligible titles will be screened by two review authors (GT, NL, AF) independently for inclusion. If there are disagreements these will be resolved by discussion and a third review author will be involved where necessary. We will obtain the full-text of any articles that are
included at the title and abstract screening stage. Each full-text will be screened by two review authors (GT, NL, AF) independently for inclusion. If there are disagreements these will be resolved by discussion and a third review author will be involved where necessary. Reasons for exclusion at the full-text examination stage will be recorded. We will translate all non-English language studies.

Data extraction and management

Two review authors will pilot the data extraction form and make appropriate changes (GT, NL).

Two review authors (two of GT, NL, AF) will in duplicate extract data independently for each study. These will be compared for each study and any disagreements will be resolved by discussion and a third review author will be involved where necessary.

We will extract the following data from each study.

- Study design
- Analysis method
- Outcome measure(s)
- Length of follow-up
- N at baseline and follow-up
- Population type
- Percentage (%) male
- Mean age (standard deviation (SD))
- Covariates adjusted for
- Motivation to quit
- Intervention(s) used (if relevant)
- Risk of bias using ROBINS-I (Sterne 2016)
- Data to calculate standardised mean difference (SMD) in mental health outcomes: for each group - mean at baseline and follow-up, mean change from baseline to follow-up, and difference in mean change from baseline to follow-up, and variance
- Data to calculate risk of mental ill-health outcomes: for each group - N participants in the control group at baseline, N participants in exposure group at baseline, N participants with mental ill-health in the exposure group at follow-up, N participants with mental ill-health in the control group at follow-up
- Sources of study funding and authors’ declarations of interests

Assessment of risk of bias in included studies

We will assess the risk of bias for each non-randomised study, and each RCT (analysed according to smoking cessation status rather than by trial arm) using ROBINS-I, which assesses studies based on risk of bias in the following domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias in measurement of outcomes, and bias in selection of the reported result (Sterne 2016).

Measures of treatment effect

SMD in change in mental health from baseline to follow-up, between those who have quit smoking and those who continue to smoke for each study. We will calculate the SMD and its variance by extracting data in order of preference for meta-analysis: 1) adjusted or unadjusted SMD (difference in change from baseline to follow-up) and measure of variation between exposure groups (preference for adjusted estimates), 2) mean change in mental health scores from baseline to follow-up and measure of variance, by exposure group, 3) mean mental health scores and measures of variance at baseline and final follow-up, by exposure group. Then using a standard formula we will calculate the mean change and its variance by exposure group (Follmann 1992), and then the SMD, using standard formulae outlined within the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Risk ratio (RR) and 95% confidence interval (CI) for mental ill-health: we will extract data to calculate the RR for mental ill-health and its variance for each study using the following formula: (number of participants with mental ill-health in the exposure group/number of participants in exposure group at baseline) divided by (number of participants with mental ill-health in the control group/number of participants in the control group at baseline).

Unit of analysis issues

We do not foresee any analysis issues.

Dealing with missing data

We will contact the corresponding authors of studies for additional data where necessary. We will report studies narratively if we cannot obtain outcome data.

Assessment of heterogeneity

We will investigate whether there appears to be any clinical or methodological heterogeneity between studies before pooling to establish whether it is appropriate to carry out meta-analysis. Where pooling does take place we will quantify statistical heterogeneity using I^2, which describes the percentage (%) of between-study variability due to heterogeneity rather than chance. We will consider an I^2 value between 50% and 75% as substantial heterogeneity, and above 75% we will assess whether it is appropriate to report a pooled analysis.

Assessment of reporting biases

We will examine funnel plots for evidence of asymmetry and conduct Egger tests for evidence of small study bias where there are 10 or more studies contributing to a comparison.

Data synthesis

We will pool the SMDs in change and measures of variance of individual studies using a generic inverse variance random-effects model. A SMD of greater than zero will indicate that quitting smoking is associated with worse mental health at follow-up.

We will pool risk ratios (RRs) and pool measures of variance calculated for individual studies using a Mantel-Haenszel random-effects meta-analysis. A RR of greater than one will indicate that people who quit smoking experience a greater risk of mental ill-health at follow-up.

We will conduct meta-analyses of the SMD and RR for each outcome separately (i.e. depression, anxiety, stress, etc.) using RevMan 2014.

Subgroup analysis and investigation of heterogeneity

Adjustment for covariates: we will compare effect estimates from studies that present adjusted and unadjusted estimates.
Motivation to quit: we will classify studies according to whether they selected participants for inclusion based on motivation to quit (i.e. participants in RCTs will be classed as motivated to quit assuming that participants enrolled in a trial to help them stop smoking). We will compare estimates resulting from these studies, and cohort studies that follow a group of people who smoke, where the majority are likely not to want to quit in the near future. If we find any studies that adjusted effect estimates for motivation to quit we will compare unadjusted and adjusted estimates.

Study design: we will compare estimates between secondary analyses of trials, classic cohort studies, and cohort studies adopting causal designs (e.g. propensity score matching, or instrumental variable analyses).

Population comparison: we will examine whether there is evidence of a difference in effect size between studies in different clinical populations (e.g. pregnancy, mental disorder, post-surgical) and the general population. This is important for those with mental disorders in particular, because poor implementation of smoking cessation interventions for people with mental illness is supported by the belief that stopping smoking will worsen their mental health.

Length of follow-up: we will examine whether there is evidence of a difference in effect estimate between studies that assessed mental health between baseline and six weeks (i.e. to ensure follow-up occurs after the acute tobacco withdrawal period), and studies that assessed to six months or more than six months. This may differ because people who achieve a difficult life goal may have a temporary improvement in mental health because of their achievement. However, should the effect persist long-term, this supports the hypothesis that smoking itself is harmful to mental health and it is ceasing smoking and not the celebration of that achievement that improves mood.

Sensitivity analysis

Loss to follow-up: we will conduct a sensitivity analysis with removal of studies in which different numbers of participants were analysed at baseline and follow-up.

Ascertainment of smoking status: we will conduct a sensitivity analysis with removal of studies that did not biochemically verify smoking status.

Psychotherapeutic/psychoactive component within cessation intervention: we will conduct a sensitivity analysis with removal of studies that offered a psychotherapeutic/psychoactive (i.e. psychotherapy or antidepressants) component within the smoking cessation intervention.

Risk of bias: We will conduct a sensitivity analysis removing studies that are at a high risk of bias.

'Summary of findings' table and GRADE

We will create a ‘Summary of findings’ table, using GRADEpro GDT software, reporting the pooled effect estimates for our primary outcomes and the social impact outcome. We will assess these outcomes according to the five GRADE considerations (Schünemann 2013; i.e. study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for these outcomes, and to draw conclusions about the certainty of the evidence within the text of the review.

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Richardson 2019

Schünemann 2013

Sheals 2016

Siri 2009

Sterne 2016

Szatkowski 2015

**Appendices**

Appendix 1. MEDLINE search strategy
1. exp "Tobacco Use Cessation"/ or exp Smoking Cessation/
2. smoking cessation.mp.
3. (reduce* or modify*) adj3 (smok* or cigar* or tobacco)).mp.
4. (quit* or stop* or give* or cease) adj3 (smok* or cigar* or tobacco)).mp.
5. Harm Reduction/ or harm reduction.mp.
6. Smoking Reduction/
7. tobacco consumption.mp.
8. cold turkey.mp.
9. Smoking Cessation Agents/
10. "Tobacco Use Cessation Devices"/
11. Electronic Nicotine Delivery Systems/
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Mental Health/ or mental health.mp.
14. Stress, Psychological/
15. psychological health.mp.
16. Resilience, Psychological/ or psychological resilience.mp.
17. Anxiety/ or anxiety.mp or Anxiety Disorders/
18. anxious.mp.
19. Depression/ or depression.mp.
20. Depressive Disorders/ or depressive.mp.
21. Emotions/ or emotion*.mp.
22. psychological process$.mp.
23. mental hygiene.mp.
24. "Quality of Life"/ or quality of life.mp.
25. (well being or well? being).mp.
26. Affect/ or affect.mp. or Affective Symptoms/
27. Adaptation, Psychological/
28. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 12 and 28
30. limit 29 to yr="2011 -Current"

CONTRIBUTIONS OF AUTHORS

GT, PA and AM conceived the study. All authors were involved in writing and editing the manuscript.

DECLARATIONS OF INTEREST

GT's salary and research activity is paid for by a Cancer Research UK Postdoctoral Fellowship (C56067/A21330) that has been paid to University of Bath.

AM is a trustee of the Society for the Study of Addiction. She has received grants from, various organisations (e.g. Cancer Research UK) whose goals are to reduce the mortality and morbidity caused by smoking and which support the implementation of a comprehensive tobacco control strategy, as well as organisations such as the NIHR. She does not receive funding from tobacco, pharmaceutical or e-cigarette companies.

AF is employed by the University of Birmingham, has been awarded grant funding from the CRUK, NIHR and Ethicon (Johnson and Johnson) researcher led funding.

NL is employed by the University of Oxford to work as Managing Editor for the Cochrane Tobacco Addiction Group (TAG). TAG’s infrastructure is funded by the NIHR. Nicola has received payment for lectures on systematic review methodology, and has been an applicant on project funding to carry out priority setting and systematic reviews in the area of tobacco control (NIHR funded). None of this is deemed a conflict of interest.

PA: none known.

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