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INTERVENTIONS FOR PREGNANT WOMEN WHO USE TOBACCO AND OTHER SUBSTANCES: A SYSTEMATIC REVIEW PROTOCOL

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Author contributions

MJ is the lead and the guarantor of this review. MJ and ABa conceptualised the review and drafted the manuscript. KMC, GG, ABa, ABr and AD provided critical input and were involved in revising the protocol. MJ developed the search strategy included in the protocol. All authors approved the final version of the manuscript and accepted accountability for all aspects of the work.

Competing interests

There are no competing interests to declare.

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Data sharing statement

Once completed, review data will be available from the corresponding author (MJ) upon request.

ABSTRACT

Introduction:

The prevalence of tobacco smoking in pregnancy remains elevated in some disadvantaged populations of women. One group is those who use alcohol and/or other psychoactive substances during pregnancy, with tobacco use prevalence estimates ranging from 71% to 95%. Although effective evidence-based cessation treatments exist, few women with co-occurring substance use problems successfully stop smoking tobacco during pregnancy. There is limited information about treatments that specifically target this group and a summary of the available research is required to assist and enhance the development of innovative cessation interventions. This article describes a protocol for a comprehensive review of studies that have trialled behavioural and/or pharmacological tobacco cessation interventions in populations of pregnant women who are nicotine dependent and use other psychoactive substances.

Methods and analysis:

The review will undertake literature searches in MEDLINE, PsycINFO, CINAHL, EMBASE and ProQuest databases, as well as the grey literature. Studies of any design methodology will be included if they describe changes to tobacco smoking behaviours in quantitative terms. Participants include pregnant women of any age, who smoke tobacco, that are seeking, are in, or have recently completed treatment for the use of psychoactive substances. Interventions are any psychological, behavioural or pharmacological treatments used to treat tobacco use. Outcome measures are any that quantitatively report abstinence or reductions in participant tobacco consumption. Key details and tobacco related outcomes from included studies will be extracted and tabulated before being narratively synthesised. The systematic review protocol has been developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.

Ethics and dissemination:

Ethics approval is not required. Findings will be disseminated via peer-reviewed literature and conference presentations.

Protocol registration number:

PROSPERO: CRD42018108777

ARTICLE SUMMARY

Strengths and limitations:

- This protocol was designed according to the Preferred Reporting Items for Systematic review and Meta-Analyses for Protocols guidelines.
- This will be the first review of smoking cessation interventions for maternal populations who experience problems with psychoactive substances.
- Results of the review will identify gaps in our current knowledge of smoking cessation for disadvantaged groups, and highlight future treatment directions.
- The review may be limited by the heterogeneity of study methodologies and outcome measures that restrict the ability to pool outcome data and assess the effectiveness of cessation treatments.

INTRODUCTION

Tobacco smoking during pregnancy is the major modifiable contributor to adverse maternal, fetal and neonatal outcomes.[1,2] Maternal smoking during pregnancy has been strongly associated with intrauterine growth restriction, ectopic pregnancy, placental abruption, placenta praevia, pre-term birth, miscarriage and stillbirth.[3,4] Infants exposed to prenatal tobacco smoking are more likely to experience low birth-weight, sudden unexpected death in infancy, chronic respiratory disorders, cardiovascular disease, obesity, attachment difficulties, learning and behavioural difficulties and have a greater likelihood of developing tobacco and other substance use disorders later in life.[4-9]

The prevalence of maternal tobacco smoking has declined significantly worldwide since 1985.[10] Estimates from 2016 suggest a global prevalence of smoking during pregnancy of 1.7% (95% CI 0.0-4.5), ranging from 0.8% (95% CI 0.0-2.2) in the African region to 8.1% (95% CI 4.0-12.2) in the European region.[10] Despite the declines in general maternal populations, elevated rates of tobacco use in pregnancy remain in some overlooked, but high-risk groups of women. One group in particular, is women who use alcohol and other psychoactive substances (including opioids, cannabis, stimulants and benzodiazepines) during pregnancy. Although population-wide tobacco smoking rates for this group are hard to find, published prevalence estimates from studies of pregnant women in substance use treatment range from 71% to 95%.[11-14] Women who describe using multiple substances are also more likely to smoke tobacco than those who use only one (OR: 2.35, 95% CI: 1.37–4.04).[14]

Pregnancy is typically viewed as a period of high motivation to cease tobacco use, driven by a protective urge to safeguard the fetus.[15] A large number of effective, evidence-based treatments exist for the general population of pregnant women to assist cessation, reflecting the significant public health concerns that surround the issue. A 2017 Cochrane review[16] assessed 102 psychosocial interventions for women to stop smoking in pregnancy that addressed the mental, social or emotional factors related to nicotine dependence. Moderate quality evidence found that these interventions increased the proportion of women who stopped smoking in late pregnancy by 35% when compared to controls.[16] Such interventions include incentive-based programs, motivational interviewing, cognitive-behavioural therapy, health education, social support and biochemical feedback on maternal and fetal nicotine exposure.[13]

Pharmacotherapies are also available to support maternal tobacco cessation. Nicotine replacement therapy (NRT), varenicline and bupropion and more recently, electronic nicotine delivery systems (e-cigarettes) used for the purpose of stopping smoking are commonly used in general populations. The combination of NRT with behavioural strategies has been shown to improve cessation outcomes when compared to outcomes from single interventions or usual care,[17] and is considered gold standard for

tobacco treatment in general populations.[18] The evidence is not as clear for pregnant women, with a 2015 Cochrane review of pharmacotherapies for smoking cessation in pregnancy finding marginal support for NRT delivered with behavioural support, suggesting that it may increase smoking abstinence by 40% in late pregnancy (RR 1.43, 95% CI 1.03 to 1.93).[19] This borderline evidence may be due to the dosages of NRT trialled being unable to counter the increased metabolism of nicotine that occurs during pregnancy[20] and recommendations for higher doses to be used in future antenatal smoking cessation studies have been made.[19]

Yet despite the availability of treatments and their effectiveness in general maternal populations, there are few pregnant women with co-occurring tobacco and substance use disorders who successfully abstain from tobacco. Poor cessation outcomes do not appear to be associated with a lack of desire to quit. Pregnant women with substance use disorders have the same urges to protect their unborn children and aspire to stop tobacco consumption at rates similar to those who do not use substances.[14,21,22] Regrettably, a range of barriers impact their ability to quit and contribute to poor outcomes when attempting to stop using currently available cessation treatments.[14,21,23-31]

Physiologically, pregnant women with substance use disorders are more likely to have a comorbid mental illness, consume greater amounts of tobacco, and experience more severe nicotine withdrawal symptoms than those without substance use disorders.[30] Smoking tobacco is also known to enhance the psychoactive effects of opioids and cannabis[23,25] while counteracting some of the adverse cognitive effects of alcohol consumption.[26,28] Socially, the cultural norms associated with tobacco smoking in this population,[24] and the high proportion of women with partners and/or other household members who smoke,[14,21] have significant impacts on cessation efforts. Systemic barriers occur at a treatment level because priority is often given to cessation of alcohol or other drug use over tobacco use during pregnancy.[27,31] The high level of support required of health care professionals to facilitate tobacco cessation in this group[14] is often prohibited by organisational and individual factors, including lack of knowledge, time, confidence and counselling skills.[29]

The absence of effective tobacco smoking treatments for pregnant women with other substance use problems and the need for aggressive targeted efforts to reduce smoking in this high-risk group has been documented.[13,32,33] A 2014 systematic review of tobacco treatments for pregnant women receiving opiate agonist treatment found three published studies.[13] Only one, a randomised controlled trial conducted in 2012 (N=102), had a significant, positive effect on smoking abstinence.[34] A 2011 prospective cohort study (n=91), significantly influenced reduction in tobacco use but not abstinence[35] and a 2004 randomised controlled trial (N=63) achieved increases in motivation to stop smoking but had no impact on cessation rates.[36] The review had no constraints on time since publication, but was limited

to interventions for pregnant women receiving opiate agonist treatment, omitting those targeting women with other substance use disorders.

A 2011 review of interventions designed to reduce or eliminate tobacco smoking during pregnancy uncovered two studies from a possible 97 that specifically targeted substance use populations.[33] The results included one of the aforementioned studies.[36] The other, a 1996 pilot study (N=34), implemented a compulsory smoking treatment in a smoke-free in-patient maternal substance use program.[37] The intervention increased motivation to stop smoking but did not assess reductions in tobacco use or cessation. This review focused on smoking treatment interventions for all pregnant women, grouping by population and only reporting studies that met predetermined ratings for methodological rigour and quality. The review was restricted to a 20-year time frame (1990-2010) and focused on research from Canada and the United States.

The current evidence suggests that there is a shortage of smoking cessation treatments targeting pregnant women with substance use disorders. Given that smoking prevalence is now greatest in groups vulnerable to social disadvantage, including those with substance use disorders,[38] and that treatment targets are now focusing on disparities in smoking rates between population groups,[39] more innovative and comprehensive cessation interventions are acutely needed. To support the future development of such treatments, an appraisal of approaches that have previously assisted smoking cessation in maternal substance use poulations, including those that have not significantly impacted abstinence, is required.

Therefore, the current review will focus on providing the most comprehensive synthesis of smoking cessation treatments for pregnant women with concurrent substance and tobacco use to date. This will be achieved by including all interventions that have been trialled in this group, regardless of participant demographic, substance of concern or time since studied.

Objectives

This review will systematically examine all studies that have trialled behavioural and/or pharmacological tobacco cessation interventions in populations of pregnant women who are nicotine dependent and use alcohol and/or other psychoactive substances. It will provide an updated summary of the evidence to date and highlight those interventions that have demonstrated effectiveness in the reduction of, or abstinence from, tobacco use in this high-priority group of women.

METHODS

The review protocol follows the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) statement,[40] and the review findings

will be reported using published PRISMA guidelines.[41] The review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/PROSPERO; registration number: CRD42018108777).

Criteria for study inclusion

Study Characteristics

Studies must offer a treatment designed to reduce or stop tobacco smoking in pregnant women with substance use concerns. For the purpose of this review, tobacco encompasses all smokable products including cigarettes, cigars, pipes and hookah's and alternative tobacco products such as electronic cigarettes. Treatments that target cannabis smoking will not be included.

Studies of any design methodology will be included, provided that they report quantitative outcomes relating to changes in tobacco smoking behaviours. Designs may be experimental or quasi-experimental, including pre-post interventions, pilot and feasibility studies. There will be no limit on year of report publication and studies may be published in any language. Abstracts written in a language other than English will be translated using Google Translate to assess eligibility. The full text of those meeting the criteria will be professionally translated. Pre-clinical or animal studies will be excluded.

Participants

Participants may be pregnant women of any age, who smoke tobacco. They must be seeking, already in, or have recently completed, treatment for the use of alcohol or other psychoactive substances.

Interventions

Interventions to be included may be any psychological, behavioural or pharmacological treatments used to treat tobacco dependence. Examples may include, but are not limited to, counselling therapies such as motivational interviewing and cognitive behavioural therapy, contingency management, pharmacotherapies including NRT, social support or self-help strategies. They may be offered in health- or community-based settings and mode of delivery may be in-person or remotely using telecommunication technologies.

Outcomes

Outcome measures will include any measure that reports abstinence or reductions in tobacco consumption of participants. These may be biochemical validation measures or self-reported measures, with or without biochemical verification. Examples of biochemical validation measures include carbon monoxide and cotinine (usually urinary or saliva), while self-report measures may include, but are not limited to, prolonged abstinence, point prevalence abstinence, continuous abstinence or number of cigarettes smoked.[42]

Information sources

Electronic databases

Literature searches for relevant published articles will be performed in the following databases: MEDLINE, PsycINFO, CINAHL, and EMBASE. The ProQuest database will be searched to identify appropriate dissertations and theses. The search strategy will include MeSH terms and keywords associated with tobacco use, pregnancy, psychoactive substance use and interventions for smoking cessation. An example of a search created for MEDLINE is available in Appendix 1. Identical search terms will be adopted for each of the remaining databases, with changes to syntax made as required.

Other sources

The following strategies will be used to obtain studies not identified through electronic database searches:

i. A manual search of the reference lists of included full-text articles
ii. A grey literature search using Google Scholar and reviewing the first 20 pages of results.
iii. Contacting experts in the specific field about research currently being conducted or unpublished study results.

Data management and collection

All identified titles and abstracts will be stored in Covidence, an electronic screening and data extraction tool recommended for Cochrane reviews.[43] Two reviewers (MJ and KM) will independently screen articles against eligibility criteria to determine inclusion status, with a comparison of results made to ensure consistency. Full articles of included abstracts will then be reviewed against the inclusion criteria by the same reviewers. Any discrepancies at either stage will be discussed and referred to a third reviewer for consensus where necessary. Articles deemed ineligible will be documented, with the reason for exclusion noted for acknowledgement in the full review.

Data extraction

All full text articles remaining after the screening process will have relevant data extracted independently by two reviewers (MJ and KM). A data extraction template will be developed based on recommendations by the Cochrane Handbook for Systematic Reviews of Interventions.[44] The template will be piloted by both reviewers on the initial two articles and amendments made if necessary.

The following data variables to be extracted include:

- Author(s), journal and year.
- Study type, recruitment setting, study design, country, recruitment setting and strategy.

- Eligibility criteria, participant demographic and clinical characteristics including primary substance consumed.
- Intervention characteristics including strategies used, delivery method, duration and follow-up.
- Study objectives, outcomes, outcome measures, analysis and results.

Additional data fields may be added to the template allowing for flexibility as required.

Assessment of risk of bias

Two reviewers (MJ and KM) will independently assess the likelihood that components of the design, method or conduct of included studies could lead to misleading or ambiguous results. This will be evaluated using the Effective Public Health Project (EPHPP) quality assessment tool for quantitative studies.[45] This tool was designed to enhance the systematic review process, particularly in the public health arena. It has been assessed to have both content and construct reliability and intra-rater reliability.[45] The following components will be rated for each study: selection bias; study design; confounders; blinding; data collection methods; withdrawals and dropouts; intervention integrity and data analysis; feasibility and acceptability measures; and process outcomes such as fidelity and reach. Differences in risk of bias ratings in studies will be resolved by discussion between the reviewers. Where agreement cannot be reached, a third reviewer (ABa) will adjudicate.

Data synthesis and analysis

Due to the overall small size and specificity of the target population, and the likely heterogeneity of treatment interventions and outcome measures, it is anticipated that pooling of study results will be inappropriate, and a narrative synthesis will be undertaken.

Narrative synthesis

A narrative synthesis will be completed following guidelines set out in the 'Cochrane Consumers and Communication Review Group: data synthesis and analysis'.[46] Accordingly, the following processes will be undertaken:

I. Development of a preliminary synthesis of included studies. A summary of studies and their outcomes will be grouped according to interventional type and tabulated for presentation in the final review. Descriptive statistics will be performed as and where appropriate.
II. A systematic exploration of relationships, both in the data and between studies, to establish similarities and differences in effect sizes between substance types and treatment settings.
III. Assessment of the robustness of the synthesis whereby the quality of the included studies, and of the synthesis methodologies, will be critically appraised.

Patient and public involvement

No patient or public involvement was considered for the development of this protocol.

ETHICS AND DISSEMINATION

The review will be a synthesis of research outcomes, with no primary data collection undertaken. As such, ethical approval is not required. Findings will be peer-reviewed and published with all relevant additional materials including search strategies, excluded studies and data extraction. Review outcomes will also be disseminated as conference presentations.

DISCUSSION

Tobacco use remains a significant problem in some disadvantaged groups of people, including those who are pregnant and dependent on alcohol and/or other psychoactive substances. Within this population, tobacco smoking prevalence remains unacceptably high and targeted treatments are scarce. While earlier reviews have revealed few published studies, the shift in focus towards tobacco cessation treatments for high-priority, disadvantaged groups is increasing the demand for innovative new interventions. This has created a need for the most up-to-date evidence related to effective cessation treatments for such populations.

This review will be, to our knowledge, the first comprehensive evaluation of smoking cessation studies targeting maternal populations who experience problems with psychoactive substances. With no restrictions placed on substance type, and no studies excluded due to study design, language or time since publication, this review will identify the extent of current research in this area. The information gained will assist the identification of gaps in our current knowledge and evidence, and highlight where and how future treatment resources should be directed.

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Appendix 1

#	SEARCH TERMS	RESULTS
1	"Tobacco Use Disorder"/ or Smoking Cessation/ or Smoking/ or Smoking Prevention/	154462
2	NICOTINE/ or ELECTRONIC NICOTINE DELIVERY SYSTEMS/ or NICOTINE CHEWING GUM/	25703
3	Tobacco/ or CIGAR SMOKING/ or Tobacco Products/	31379
4	(smok* or cigar* or tobacco or nicotine).tw.	320275
5	1 or 2 or 3 or 4	360278
6	Pregnancy/	828174
7	Prenatal Care/ or PREGNANT WOMEN/ or Pregnancy Complications/	112050
8	MATERNAL EXPOSURE/ or MATERNAL BEHAVIOR/ or MATERNAL HEALTH/	19307
9	(pregnan* or maternal or prenatal).tw.	631303
10	6 or 7 or 8 or 9	1036218
11	Behavior Therapy/ or contingency management.mp. or Token Economy/	27522
12	Financial Incentives.mp.	3503
13	Social Support/	64890
14	Counseling/	33462
15	Motivational interviewing/	1375
16	Self-Help Groups/	8694
17	"Reinforcement (Psychology)"/	16203
18	PSYCHOTHERAPY/ or PSYCHOTHERAPY, GROUP/ or PSYCHOTHERAPY, BRIEF/	65389
19	Cognitive Therapy/	22398
20	(Intervention* or treatment* or therap* or program*).tw,kw,kf.	6536631
21	pharmacotherapy.mp. or Drug Therapy/	55714
22	*Hotlines/ or quitline.mp.	2065
23	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	6658208
24	Alcohol Drinking/	62313
25	amphetamine/ or methamphetamine/	20152
26	COCAINE-RELATED DISORDERS/ or COCAINE/ or CRACK COCAINE/ or COCAINE SMOKING/	28630
27	CANNABIS/	8060
28	benzodiazepine/	20826
29	(Heroin or mari?uana or opioid* or opiate* or alcohol* or cannabis).tw.	414686
30	Analgesics, Opioid/	37927
31	HEROIN DEPENDENCE/ or HEROIN/	12619
32	METHADONE/	11687
33	substance-related disorders/ or alcohol-related disorders/ or amphetamine-related disorders/ or cocaine-related disorders/ or drug overdose/ or heroin dependence/ or inhalant abuse/ or marijuana abuse/ or neonatal abstinence syndrome/ or opioid-related disorders/ or phencyclidine abuse/ or psychoses, substance-induced/ or substance abuse, intravenous/ or substance abuse, oral/	147980
34	Drug abuse.mp.	16604
35	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	591403
36	5 and 10 and 23 and 35	1564
37	animals/ not (humans/ and animals/)	4475642
38	36 not 37	1536

#	SEARCH TERMS	RESULTS
1	"Tobacco Use Disorder"/ or Smoking Cessation/ or Smoking/ or Smoking Prevention/	154462
2	NICOTINE/ or ELECTRONIC NICOTINE DELIVERY SYSTEMS/ or NICOTINE CHEWING GUM/	25703
3	Tobacco/ or CIGAR SMOKING/ or Tobacco Products/	31379
4	(smok* or cigar* or tobacco or nicotine).tw.	320275
5	1 or 2 or 3 or 4	360278
6	Pregnancy/	828174
7	Prenatal Care/ or PREGNANT WOMEN/ or Pregnancy Complications/	112050
8	MATERNAL EXPOSURE/ or MATERNAL BEHAVIOR/ or MATERNAL HEALTH/	19307
9	(pregnan* or maternal or prenatal).tw.	631303
10	6 or 7 or 8 or 9	1036218
11	Behavior Therapy/ or contingency management.mp. or Token Economy/	27522
12	Financial Incentives.mp.	3503
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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	2
Sponsor	5b	Provide name for the review funder and/or sponsor	2
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	2
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8-9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	n/a
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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INTERVENTIONS FOR PREGNANT WOMEN WHO USE TOBACCO AND OTHER SUBSTANCES: A SYSTEMATIC REVIEW PROTOCOL

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Keywords:	Smoking cessation, Pregnancy, Tobacco use disorder, Substance use disorder, Disadvantaged populations

INTERVENTIONS FOR PREGNANT WOMEN WHO USE TOBACCO AND OTHER SUBSTANCES: A SYSTEMATIC REVIEW PROTOCOL

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Keywords:

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Author contributions

MJ is the lead and the guarantor of this review. MJ and ABa conceptualised the review and drafted the manuscript. KMC, GG, ABa, ABr and AD provided critical input and were involved in revising the protocol. MJ developed the search strategy included in the protocol. All authors approved the final version of the manuscript and accepted accountability for all aspects of the work.

Competing interests

There are no competing interests to declare.

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Data sharing statement

Once completed, review data will be available from the corresponding author (MJ) upon request.

ABSTRACT

Introduction:

The prevalence of tobacco smoking in pregnancy remains elevated in some disadvantaged populations of women. One group is those who use alcohol and/or other psychoactive substances during pregnancy, with tobacco use prevalence estimates ranging from 71% to 95%. Although effective evidence-based cessation treatments exist, few women with co-occurring substance use problems successfully stop smoking during pregnancy. There is limited information about treatments that specifically target this group and a summary of the available research is required to assist and enhance the development of innovative cessation interventions. This article describes a protocol for a comprehensive review of studies that have trialled behavioural and/or pharmacological tobacco cessation interventions in populations of pregnant women who are nicotine dependent and use other psychoactive substances.

Methods and analysis:

The review will undertake literature searches in MEDLINE, PsycINFO, CINAHL, EMBASE and ProQuest databases, as well as the grey literature. Studies of any design methodology will be included if they describe changes to tobacco smoking behaviours in quantitative terms. No restriction on year of publication or published language will apply. Participants include pregnant women of any age, who smoke tobacco, that are seeking or having treatment, or in post-treatment recovery for the use of psychoactive substances. Interventions are any psychological, behavioural or pharmacological treatments used to treat tobacco use. Outcome measures are any that quantitatively report abstinence or reductions in participant tobacco consumption. Key details and tobacco related outcomes from included studies will be extracted and tabulated before being narratively synthesised. The systematic review protocol has been developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.

Ethics and dissemination:

Ethics approval is not required. Findings will be disseminated via peer-reviewed literature, conference presentations, media and social media.

Protocol registration number:

PROSPERO: CRD42018108777

ARTICLE SUMMARY

Strengths and limitations:

- This protocol was designed according to the Preferred Reporting Items for Systematic review and Meta-Analyses for Protocols (PRISMA-P) guidelines.
- The review will be strengthened methodologically by independent double screening and data extraction and the use of the Effective Public Health Practice Project (EPHPP) quality assessment tool.
- A broad search strategy has been devised, including a search of the grey literature, to capture all possible trialled interventions that fall within the scope of this review.
- The review may be limited by the heterogeneity of study methodologies and outcome measures that restrict the ability to pool outcome data and assess the effectiveness of cessation treatments.

INTRODUCTION

Tobacco smoking during pregnancy is the major modifiable contributor to adverse maternal, fetal and neonatal outcomes.[1,2] Maternal smoking during pregnancy has been strongly associated with intrauterine growth restriction, ectopic pregnancy, placental abruption, placenta praevia, pre-term birth, miscarriage and stillbirth.[3,4] Infants exposed to prenatal tobacco smoking are more likely to experience low birth-weight, sudden unexpected death in infancy, chronic respiratory disorders, cardiovascular disease, obesity, attachment difficulties, learning and behavioural difficulties and have a greater likelihood of developing tobacco and other substance use disorders later in life.[4-9]

The prevalence of maternal tobacco smoking has declined significantly worldwide since 1985.[10] Estimates from 2016 suggest a global prevalence of smoking during pregnancy of 1.7% (95% CI 0.0-4.5), ranging from 0.8% (95% CI 0.0-2.2) in the African region to 8.1% (95% CI 4.0-12.2) in the European region.[10] Despite the declines in general maternal populations, elevated rates of tobacco use in pregnancy remain in some overlooked, but high-risk groups of women. One group in particular, is women who use alcohol and other psychoactive substances (including opioids, cannabis, stimulants and benzodiazepines) during pregnancy. Although population-wide smoking rates for this group are hard to find, published prevalence estimates from studies of pregnant women in substance use treatment range from 71% to 95%.[11-14] Women who describe using multiple substances are also more likely to smoke tobacco than those who use only one (OR: 2.35, 95% CI: 1.37–4.04).[14]

Pregnancy is typically viewed as a period of high motivation to cease tobacco use, driven by a protective urge to safeguard the fetus.[15] A large number of effective, evidence-based treatments exist for the general population of pregnant women to assist cessation, reflecting the significant public health concerns that surround the issue. A 2017 Cochrane review[16] assessed 102 psychosocial interventions for women to stop smoking in pregnancy that addressed the mental, social or emotional factors related to nicotine dependence. Moderate quality evidence found that these interventions increased the proportion of women who stopped smoking in late pregnancy by 35% when compared to controls.[16] Such interventions include incentive-based programs, motivational interviewing, cognitive-behavioural therapy, health education, social support and biochemical feedback on maternal and fetal nicotine exposure.[13]

Pharmacotherapies are also available to support maternal tobacco cessation. Nicotine replacement therapy (NRT), varenicline and bupropion and more recently, electronic nicotine delivery systems (ENDS; e.g. electronic cigarettes) used for the purpose of stopping smoking are commonly used in general populations. The combination of NRT with behavioural strategies has been shown to improve cessation outcomes when compared to outcomes from single interventions or usual care,[17] and is

considered gold standard for tobacco treatment in general populations.[18] The evidence is not as clear for pregnant women, with a 2015 Cochrane review of pharmacotherapies for smoking cessation in pregnancy finding marginal support for NRT delivered with behavioural support, suggesting that it may increase smoking abstinence by 40% in late pregnancy (RR 1.43, 95% CI 1.03 to 1.93).[19] This borderline evidence may be due to the dosages of NRT trialled being unable to counter the increased metabolism of nicotine that occurs during pregnancy[20] and recommendations for higher doses to be used in future antenatal smoking cessation studies have been made.[19] Support for the use of ENDS, buproprion or varenicline as an aid for cessation is limited in pregnancy, with the same 2015 review reporting only one small trial of bupropion and none of varenicline or ENDS.[19]

Yet despite the availability of treatments and their effectiveness in general maternal populations, there are few pregnant women with co-occurring tobacco and substance use disorders who successfully abstain from tobacco. Poor cessation outcomes do not appear to be associated with a lack of desire to quit. Pregnant women with substance use disorders have the same urges to protect their unborn children and aspire to stop tobacco consumption at rates similar to those who do not use substances.[14,21,22] Regrettably, a range of barriers impact their ability to quit and contribute to poor outcomes when attempting to stop using currently available cessation treatments.[14,21,23-31]

Physiologically, pregnant women with substance use disorders are more likely to have a comorbid mental illness, consume greater amounts of tobacco, and experience more severe nicotine withdrawal symptoms than those without substance use disorders.[30] Smoking tobacco is also known to enhance the psychoactive effects of opioids and cannabis[23,25] while counteracting some of the adverse cognitive effects of alcohol consumption.[26,28] Socially, the cultural norms associated with tobacco smoking in this population,[24] and the high proportion of women with partners and/or other household members who smoke,[14,21] have significant impacts on cessation efforts. Systemic barriers occur at a treatment level because priority is often given to cessation of alcohol or other drug use over tobacco use during pregnancy.[27,31] The high level of support required of health care professionals to facilitate tobacco cessation in this group[14] is often prohibited by organisational and individual factors, including lack of knowledge, time, confidence and counselling skills.[29]

The absence of effective tobacco smoking treatments for pregnant women with other substance use problems and the need for aggressive targeted efforts to reduce smoking in this high-risk group has been documented.[13,32,33] A 2014 systematic review of tobacco treatments for pregnant women receiving opiate agonist treatment found three published studies.[13] Only one, a randomised controlled trial conducted in 2012 (N=102), had a significant, positive effect on smoking abstinence.[34] A 2011 prospective cohort study (n=91), significantly influenced reduction in tobacco use but not abstinence[35] and a 2004 randomised controlled trial (N=63) achieved increases in motivation to stop smoking but had

no impact on cessation rates.[36] The review had no constraints on time since publication, but was limited to interventions for pregnant women receiving opiate agonist treatment, omitting those targeting women with other substance use disorders.

A 2011 review of interventions designed to reduce or eliminate tobacco smoking during pregnancy uncovered two studies from a possible 97 that specifically targeted substance use populations.[33] The results included one of the aforementioned studies.[36] The other, a 1996 pilot study (N=34), implemented a compulsory smoking treatment in a smoke-free in-patient maternal substance use program.[37] The intervention increased motivation to stop smoking but did not assess reductions in tobacco use or cessation. This review focused on smoking treatment interventions for all pregnant women, grouping by population and only reporting studies that met predetermined ratings for methodological rigour and quality. The review was restricted to a 20-year time frame (1990-2010) and focused on research from Canada and the United States.

The current evidence suggests that there is a shortage of smoking cessation treatments targeting pregnant women with substance use disorders. Given that smoking prevalence is now greatest in groups vulnerable to social disadvantage, including those with substance use disorders,[38] and that treatment targets are now focusing on disparities in smoking rates between population groups,[39] more innovative and comprehensive cessation interventions are acutely needed. To support the future development of such treatments, an appraisal of approaches that have previously assisted smoking cessation in maternal substance use poulations, including those that have not significantly impacted abstinence, is required.

Therefore, the current review will focus on providing the most comprehensive synthesis of smoking cessation treatments for pregnant women with concurrent substance and tobacco use to date. This will be achieved by including all interventions that have been trialled in this group, regardless of participant demographic, substance of concern or time since studied.

Objectives

This review will systematically examine all studies that have trialled behavioural and/or pharmacological tobacco cessation interventions in populations of pregnant women who are nicotine dependent and use alcohol and/or other psychoactive substances. It will provide an updated summary of the evidence to date and highlight those interventions that have demonstrated effectiveness in the reduction of, or abstinence from, tobacco use in this high-priority group of women.

METHODS

The review protocol follows the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) statement,[40] and the review findings will be reported using published PRISMA guidelines.[41] The review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/PROSPERO; registration number: CRD42018108777).

Criteria for study inclusion

Study Characteristics

Studies must offer a treatment designed to reduce or stop tobacco smoking in pregnant women with substance use concerns. For the purpose of this review, tobacco encompasses all smokable products including cigarettes, cigars, pipes and hookah's. Treatments that target a combination of tobacco and cannabis use will be included but those that specifically target cannabis smoking will not.

Studies of any design methodology will be included, provided that they report quantitative outcomes relating to changes in tobacco smoking behaviours. Designs may be experimental or quasi-experimental, including pre-post interventions, pilot and feasibility studies. There will be no limit on year of report publication and studies may be published in any language. Abstracts written in a language other than English will be translated using Google Translate to assess eligibility. The full text of those meeting the criteria will be professionally translated. Pre-clinical or animal studies will be excluded.

Participants

Participants may be pregnant women of any age, who smoke tobacco. They must be seeking or having treatment, or in post-treatment recovery for the use of alcohol and/or other psychoactive substances.

Interventions

Interventions to be included may be any psychological, behavioural or pharmacological treatments used to treat tobacco dependence, including the use of ENDS to reduce or aid smoking cessation. Examples may include, but are not limited to, counselling therapies such as motivational interviewing and cognitive behavioural therapy, contingency management, social support or self-help strategies and pharmacotherapies including NRT and electronic cigarettes. They may be offered in health- or community-based settings and mode of delivery may be in-person or remotely using telecommunication technologies.

Outcomes

Outcome measures will include any measure that reports abstinence or reductions in tobacco consumption of participants. These may be biochemical validation measures or self-reported measures, with or without biochemical verification. Examples of biochemical validation measures include carbon monoxide and cotinine (usually urinary or saliva), while self-report measures may include, but are not limited to, prolonged abstinence, point prevalence abstinence, continuous abstinence or number of cigarettes smoked.[42]

Information sources

Electronic databases

Literature searches for relevant published articles will be performed in the following databases: MEDLINE, PsycINFO, CINAHL, and EMBASE. The ProQuest database will be searched to identify appropriate dissertations and theses. The search strategy will include MeSH terms and keywords associated with tobacco use, pregnancy, psychoactive substance use and interventions for smoking cessation. An example of a search created for MEDLINE is available as online supplementary material. Identical search terms will be adopted for each of the remaining databases, with changes to syntax made as required.

Other sources

The following strategies will be used to obtain studies not identified through electronic database searches:

i. A manual search of the reference lists of included full-text articles
ii. A grey literature search using Google Scholar and reviewing the first 20 pages of results.
iii. Contacting experts in the specific field about research currently being conducted or unpublished study results.

Data management and collection

All identified titles and abstracts will be stored in Covidence, an electronic screening and data extraction tool recommended for Cochrane reviews.[43] Two reviewers (MJ and KM) will independently screen articles against eligibility criteria to determine inclusion status, with a comparison of results made to ensure consistency. Full articles of included abstracts will then be reviewed against the inclusion criteria by the same reviewers. Any discrepancies at either stage will be discussed and referred to a third reviewer for consensus where necessary. Articles deemed ineligible will be documented, with the reason for exclusion noted for acknowledgement in the full review.

Data extraction

All full text articles remaining after the screening process will have relevant data extracted independently by two reviewers (MJ and KM). A data extraction template will be developed based on recommendations by the Cochrane Handbook for Systematic Reviews of Interventions.[44] The template will be piloted by both reviewers on the initial two articles and amendments made if necessary.

The following data variables to be extracted include:

- Author(s), journal and year.
- Study type, recruitment setting, study design, country, recruitment setting and strategy.
- Eligibility criteria, participant demographic and clinical characteristics including primary substance consumed.
- Intervention characteristics including strategies used, delivery method, duration and follow-up.
- Study objectives, outcomes, outcome measures, analysis and results.

Additional data fields may be added to the template allowing for flexibility as required.

Assessment of risk of bias

Two reviewers (MJ and KM) will independently assess the likelihood that components of the design, method or conduct of included studies could lead to misleading or ambiguous results. This will be evaluated using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies.[45] This tool was designed to enhance the systematic review process, particularly in the public health arena. It has been assessed to have both content and construct reliability and intra-rater reliability.[45] The following components will be rated for each study: selection bias; study design; confounders; blinding; data collection methods; withdrawals and dropouts; intervention integrity and data analysis; feasibility and acceptability measures; and process outcomes such as fidelity and reach. Differences in risk of bias ratings in studies will be resolved by discussion between the reviewers. Where agreement cannot be reached, a third reviewer (ABa) will adjudicate.

Data synthesis and analysis

Due to the overall small size and specificity of the target population, and the likely heterogeneity of treatment interventions and outcome measures, it is anticipated that pooling of study results will be inappropriate, and a narrative synthesis will be undertaken.

Narrative synthesis

A narrative synthesis will be completed following guidelines set out in the 'Cochrane Consumers and Communication Review Group: data synthesis and analysis'.[46] Accordingly, the following processes will be undertaken:

I. Development of a preliminary synthesis of included studies. A summary of studies and their outcomes will be grouped according to interventional type and tabulated for presentation in the final review. Descriptive statistics will be performed as and where appropriate.

II. A systematic exploration of relationships, both in the data and between studies, to establish similarities and differences in effect sizes between substance types and treatment settings.

III. Assessment of the robustness of the synthesis whereby the quality of the included studies, and of the synthesis methodologies, will be critically appraised.

Patient and public involvement

Patient or public involvement was not considered appropriate for the development of this protocol as it involves no patient recruitment or use of individual participant data.

ETHICS AND DISSEMINATION

The review will be a synthesis of research outcomes, with no primary data collection undertaken. As such, ethical approval is not required. Findings will be peer-reviewed and published with all relevant additional materials including search strategies, excluded studies and data extraction. Review outcomes will also be disseminated as conference presentations, in the media and via appropriate social media platforms.

DISCUSSION

Tobacco use remains a significant problem in some disadvantaged groups of people, including those who are pregnant and dependent on alcohol and/or other psychoactive substances. Within this population, tobacco smoking prevalence remains unacceptably high and targeted treatments are scarce. While earlier reviews have revealed few published studies, the shift in focus towards tobacco cessation treatments for high-priority, disadvantaged groups is increasing the demand for innovative new interventions. This has created a need for the most up-to-date evidence related to effective cessation treatments for such populations.

This review will be, to our knowledge, the first comprehensive evaluation of smoking cessation studies targeting maternal populations who experience problems with psychoactive substances. With no restrictions placed on substance type, and no studies excluded due to study design, language or time since publication, this review will identify the extent of current research in this area. The information gained will assist the identification of gaps in our current knowledge and evidence, and highlight where and how future treatment resources should be directed.

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	Searches	Results
1	"Tobacco Use Disorder"/ or Smoking Cessation/ or Smoking/ or Smoking Prevention/	158251
2	NICOTINE/ or NICOTINE CHEWING GUM/	24782
3	Tobacco/ or CIGAR SMOKING/ or Tobacco Products/	32839
4	(smok* or cigar* or tobacco or nicotine).tw.	335945
5	1 or 2 or 3 or 4	376646
6	Pregnancy/	851009
7	Prenatal Care/ or PREGNANT WOMEN/ or Pregnancy Complications/	116035
8	MATERNAL EXPOSURE/ or MATERNAL BEHAVIOR/ or MATERNAL HEALTH/	20525
9	(pregnan* or maternal or prenatal).tw.	657499
10	6 or 7 or 8 or 9	1069331
11	Behavior Therapy/ or contingency management.mp. or Token Economy/	28234
12	Financial Incentives.mp.	3777
13	Social Support/	67543
14	Counseling/	34474
15	Motivational interviewing/	1575
16	Self-Help Groups/	8889
17	"Reinforcement (Psychology)"/	16654
18	PSYCHOTHERAPY/ or PSYCHOTHERAPY, GROUP/ or PSYCHOTHERAPY, BRIEF/	66866
19	Cognitive Therapy/	23854
20	(intervention* or treatment* or therap* or program*).tw,kw,kf.	6880697
21	pharmacotherapy.mp. or Drug Therapy/	57657
22	*Hotlines/ or quitline.mp.	2148
23	ELECTRONIC NICOTINE DELIVERY SYSTEMS/	2579
24	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	7008545
25	Alcohol Drinking/	64393
26	amphetamine/ or methamphetamine/	20649
27	COCAINE-RELATED DISORDERS/ or COCAINE/ or CRACK COCAINE/ or COCAINE SMOKING/	29187
28	CANNABIS/	8561
29	benzodiazepine/	21203
30	(heroin or mari?uana or opioid* or opiate* or alcohol* or cannabis).tw.	435671
31	Analgesics, Opioid/	40711
32	HEROIN DEPENDENCE/ or HEROIN/	12848
33	METHADONE/	11968
34	substance-related disorders/ or alcohol-related disorders/ or amphetamine-related disorders/ or cocaine-related disorders/ or drug overdose/ or heroin dependence/ or inhalant abuse/ or marijuana abuse/ or neonatal abstinence syndrome/ or opioid-related disorders/ or phencyclidine abuse/ or psychoses, substance-induced/ or substance abuse, intravenous/ or substance abuse, oral/	153101
35	drug abuse.mp.	17165
36	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	616691
37	5 and 10 and 24 and 36	1666
38	animals/ not (humans/ and animals/)	4580602
39	37 not 38	1637

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	2
Sponsor	5b	Provide name for the review funder and/or sponsor	2
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	2
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8-9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	n/a
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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