BMJ Open

Association between vaping and health outcomes in patients with opioid use disorder: A systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040349
Article Type:	Protocol
Date Submitted by the Author:	11-May-2020
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Keywords:	MENTAL HEALTH, Substance misuse < PSYCHIATRY, STATISTICS & RESEARCH METHODS

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Title: Association between vaping and health outcomes in patients with opioid use disorder: A systematic review protocol

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ABSTRACT

Introduction

Vaping behaviour has increased in popularity and is particularly important to examine how it effects health outcomes in vulnerable populations, including those with opioid use disorder (OUD). With poly-substance use including cigarette and cannabis use being highly prevalent in the OUD population and cannabis/nicotine increasingly being consumed by vaping, vaping may have an important contribution to health outcomes in these individuals. The primary objective of this review is to systematically assess the literature related to patients with OUD and the effects vaping has shown on their physical and mental health.

Method and Analysis

A systematic search of databases including MEDLINE, EMBASE, PsycINFO, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Cochrane Clinical Trials Registry, the National Institutes for Health Clinical Trials Registry and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) will be conducted. Identified citations will be screened by two reviewers to determine eligibility at the title and abstract level, and then at the full-text and data extraction phases. Any disagreements in inclusion will be resolved through unblinded discussion by these reviewers, with any remaining disagreements being resolved by a third reviewer. Data will be conducted according to the data extraction form tested prior to abstraction. Included studies will be examined for quality and bias and will be meta-analysed where applicable. This protocol is reported in keeping with the PRISMA-P guidelines.

Ethics and Dissemination

The results for this review will be disseminated through posters and presentations at scientific conferences. Additionally, we are collaborating with the Canadian Addiction Treatment Centre (CATC) clinics to help disseminate the findings for this review.

Systematic Review Registration: The systematic review has been submitted to PROSPERO (Submission number 178441) and is awaiting registration.

ARTICLE SUMMARY

Strengths and limitations of this study

Strengths

- To our knowledge, this will be the first systematic review examining the association between vaping and health outcomes in the OUD population.
- We aim to conduct additional analyses examining mortality, overdoses, hospitalizations, and emergency room visits related to vaping.

Limitations

- This review may be limited in the number of articles identified that are investigating vaping and health outcomes in the OUD population.

Key words: systematic review protocol, vaping, opioid use disorder, health outcomes

Manuscript Word Count: 1934

INTRODUCTION

Rationale

Vaping behaviour has increased in popularity, raising many questions about short- and long-term health outcomes given the scarcity of evidence and methodological investigations. Vaping is described as inhaling and exhaling a product which is referred to as a vapor[1]. Vapours are aerosols derived from the heating of a substance, most typically being comprised of nicotine, flavours, and recently, cannabis[2,3]. One of the most commonly known and used vaping devices is the e-cigarette which was initially introduced to the public as being a healthier alternative to smoking a combustible cigarette[4]. However, increasing evidence suggests that e-cigarettes release other toxins such as volatile organic compounds, and carbonyls that are not only dangerous to the individuals vaping, but also have potential for second and thirdhand smoking[5,6].

Vaping has gained traction amongst Canadians as a less harmful alternative to cigarettes[7]. The number of individuals between 16-19 years of age who report having ever vaped increased from 29.3% to 37.0% between 2017 and 2018, with the proportion of individuals having vaped 15 days or more within 30 days rising from 2.1% to 3.6% in the same time[8]. While supporters of vaping might suggest increases can be explained by increased uptake of vaping as a substitution for cigarettes in a long-range attempt to quit smoking, evidence indicates that the upward trend in vaping is observed most strongly among those who identify as "never" or "experimental" smokers[8]. As vaping substances such as nicotine or cannabis maintains their addictive properties, this behavior presents a concern for at-risk populations, including those with opioid use disorder (OUD).

Patients with OUD are at greater risk of polysubstance use, as well as physical and mental health co-morbidities[9,10]. Both cigarette smoking and cannabis use are highly prevalent in this population and it remains important to examine the impact of vaping on these patients. Preliminary results from a study investigating pharmacogenetics of OUD in patients receiving medication assisted treatment (MAT) reported nearly 19.2% of individuals with OUD report use of vaping products, with the majority being men (56%). Nicotine vaping was reported by 74% of participants; 33% reported vaping cannabis (THC, CBD, Marijuana and shatter). 11% reported vaping cannabis and nicotine, and 5.5% reported vaping water or "flavour"[11].

The high prevalence of vaping within this population, in addition to a greater susceptibility toward mental and physical health challenges, necessitates further investigation of the impact of vaping on health outcomes. The primary objective of this study is to systematically review literature pertaining to vaping in patients with OUD in order to extract known health outcomes and identify gaps to inform future studies. We hypothesize that vaping will be associated with negative health outcomes in the OUD population.

Objectives

The objective of this systematic review is to is examine and synthesise the literature investigating the association between vaping and various health outcomes in patients with OUD.
Specifically, we aim to:

1. Summarize the literature examining the association between vaping behaviour and health outcomes in patients with OUD (primary outcomes: physical and mental health conditions

related to vaping, secondary outcomes: mortality, overdoses, hospitalizations, and emergency room visits related to vaping)
2. If possible, pool studies together to conduct a meta-analysis
3. Conduct sub-group analyses based on age, sex, gender, country, study setting, and type of substance vaped and treatment status of OUD (receiving treatment vs. not receiving treatment)

METHODS AND ANALYSIS

This protocol was reported using the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guideline[12].

Eligibility criteria

The included studies will be randomized control trials (RCT) and observational studies that investigate the association between vaping and health outcomes in the OUD population. We will also include any relevant case studies or case series which will then be qualitatively reported. Studies will be excluded if they are incomplete (e.g., ongoing trials, preliminary reports) or are using animal subjects. In the case of multiple RCT papers published under a single trial registration number, we will include the most recent paper that is relevant to the systematic review.

Studies taking place in community-based settings, and in hospital, including in-patient, out-patient and emergency settings, will be assessed. No restrictions will be made on age, sex, gender, language, country, study population or study design.

Outcomes and prioritization

The primary objective of this systematic review is to identify the health outcomes associated with vaping in patients with OUD. For example, these outcomes may include physical health conditions such as cardiovascular health, pain conditions, respiratory health (including any acute respiratory syndromes' effects) or mental health conditions such as other substance use disorders, depression, and anxiety disorders. The secondary outcomes for this review include mortality, overdoses, emergency room visits and hospitalizations associated with vaping in patients with OUD.

Information sources

For this review, we will be searching all relevant search engines for RCTs and observational studies including: MEDLINE, EMBASE, PsycINFO, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Cochrane Clinical Trials Registry, the National Institutes for Health Clinical Trials Registry and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). Additionally, to identify related grey literature, we will search thesis dissertations databases and reference lists of included studies will be searched for additional articles and resources.
A health sciences librarian (SS) will be consulted when creating the search strategies for the various databases identified. A broad search strategy will be employed to include titles, abstracts, and keyword fields. The included terms in the search strategy are related to OUD and vaping. We present the search strategy for one of the included databases (Table 1) and will include the

complete table of search strategies for all databases in the full review. These databases will be searched from inception to present, without language or demographic constraints, and will be limited to human studies.

Table 1. Search strategy

Database	Search Strategy
MEDLINE	1. exp Opioid-Related Disorders/ 2. exp Heroin Dependence/ 3. exp Substance-Related Disorders/ 4. ((opiate* or opioid* or heroin* or oxyco* or codeine* or dilaudid or fentanyl or drug* or substance*) adj2 (use* or using or misuse* or abus* or dependence* or dependent* or addict*)).ti,ab. 5. exp Vaping/ 6. exp Electronic Nicotine Delivery Systems/ 7. electronic nicotine delivery system* 8. e-cigarette* (truncate) 9. electronic cigarette* 10. vape* (get vapes) 11. vape.mp. 12. vaping.mp. 13. e cigarette.mp. 14. 1 or 2 or 3 or 4 15. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 16. 14 and 15 limit 16 to humans

Data management

We will use the online platform Covidence to manage references at all stages of the review[13]. Reviewers will be trained on how to use this tool, and this protocol will be shared with all reviewers. Additionally, we will conduct a calibration stage with 50 articles to ensure team members are in agreement for the review criteria.

Selection process

All three stages of the review (title and abstract screening, full text screening, data extraction) will be conducted in duplicate. Any disagreements for inclusion of a study will be resolved through unblinded discussion by these reviewers, with any remaining disagreements being resolved by a third, graduate-level, reviewer. The recommended flow diagram for systematic reviews in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14] will be provided which will list the reasons for inclusion/exclusion. Covidence will be used in all stages of the study selection process including identifying existing duplicates and article organization[13].

Data collection process

The data extraction forms will be created and completed on Covidence and conducted in duplicate. The following items will be collected for each article included for data extraction: author, year, country of origin, population, number of participants (including number of males and females, and number assigned to each group of study), control groups used, and participant demographic details including mean age, and ethnicity. Information on how the authors collected data pertaining to vaping will be noted, including the use of self-report data or validated substance use questionnaires, and type of health outcome reported. For all outcomes, we will also note how they are defined, measured, and the frequency of measurement. If information from an included study is missing, we will contact the authors to obtain that information and keep a log of any correspondence.

Risk of bias in individual studies

All studies included in the data extraction phase will be assessed for risk of bias using appropriate tools corresponding to study design. Such assessments will be completed in duplicate. For RCTs, we will use the Cochrane Risk of Bias Tool[15] and for observational studies, we will use the Newcastle-Ottawa Scale[16]. If possible, on papers that have scored a low risk of bias, we will conduct a sensitivity analysis.

Data synthesis

The identified RCTs and observational studies will be qualitatively reported. If possible, we will conduct meta-analyses for our primary and secondary outcomes, pooling studies with similar study designs and outcome measurements and presenting results using forest plots. We will use a random-effects model which will take between-study and within-study variance into account as opposed to a fixed-effect model to account for expected heterogeneity. We will assess heterogeneity using the I^2 statistic and 95% confidence interval. We will use the Cochrane recommendation of a I^2 statistic >40% indicating high heterogeneity[17]. Anticipated sources of heterogeneity include age, sex, treatment status, and country, for which we will conduct subgroup analyses. We will also conduct subgroup analyses based on the type of substance that is vaped (i.e. cannabis, nicotine, water flavour). All quantitative analyses will be conducted on RevMan 5.3[18]. Any identified case reports or case series will be qualitatively summarized.

Meta- bias(es)

To address any publication bias, we will conduct an Eggers test if appropriate.

Data Statement
Any additional data can be made available upon request when the review is complete.

Confidence in cumulative evidence
We will utilize the grading of recommendations, assessment, development and evaluation (GRADE) framework to assess the quality of the evidence[19]. This framework will assess the risk of bias, publication bias, consistency, directness and accuracy of the literature.

Patient and Public Involvement
There will be no patient or public involvement for this systematic review.

ETHICS AND DISSEMINATION
The completed systematic review will have a knowledge dissemination component. We will have clinicians, researchers, people that vape as users of this information. We will collaborate with the Canadian Addiction Treatment Centres (CATC), an organization that delivers MAT for the OUD population, to disseminate our findings. We plan to make our findings available to healthcare professionals in various settings through summary reports and resources that will be convenient to access. We will also publish this systematic review in a peer-reviewed journal and present our findings in relevant conferences to the scientific community.

AUTHOR CONTRIBUTIONS
NS and AD: contributed to the conception and design of the study, development of data extraction forms, search strategy, manuscript writing and final review of the manuscript. SS: contributed to the development of the search strategy and final review of the manuscript. FK: contributed to the critical revision and final review of the manuscript. CS: contributed to the critical revision and final review of the manuscript. RD: contributed to the critical revision and final review of the manuscript. LT: contributed to the critical revision and final review of the manuscript. ZS: contributed to the conception and design of the study, critical revision and final approval of the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS
None.

COMPETING INTERESTS
The authors have no competing interests to declare.

FUNDING
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Dr. Samaan is supported by grants from CIHR Awards #156306 and#155404.

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

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		Reporting Item	Page Number
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	NA
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1 and 7
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	NA
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	7
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	7
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
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	4
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	4
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	5
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Study records - 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)	5

Study records - 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	5
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	6
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
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	6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	6
Data synthesis	#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 I2, Kendall's τ)	6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040349.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Dec-2020
Complete List of Authors:	Sanger, Nitika; McMaster University Faculty of Health Sciences, Medical Science Gradaute Program D'Elia, Alessia Sanger, Stephanie; McMaster University Faculty of Health Sciences, Health Sciences Library Rosic, Tea; McMaster University Samaan, M. Constantine; McMaster University Faculty of Health Sciences, Pediatrics Kapczinski, Flavio; McMaster University, de Souza, Russell; McMaster University Faculty of Health Sciences Thabane, Lehana ; McMaster University Department of Clinical Epidemiology and Biostatistics Samaan, Zainab; McMaster University Faculty of Health Sciences, Psychiatry and Behavioral Neurosciences
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Health services research
Keywords:	MENTAL HEALTH, Substance misuse < PSYCHIATRY, STATISTICS & RESEARCH METHODS

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ABSTRACT

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A systematic search of databases including MEDLINE, EMBASE, PsycINFO, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Cochrane Clinical Trials Registry, the National Institutes for Health Clinical Trials Registry and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) from inception until December 31st, 2020 will be conducted. Identified citations will be screened by two reviewers to determine eligibility at the title and abstract level, and then at the full-text and data extraction phases. Any disagreements in inclusion will be resolved through unblinded discussion by these reviewers, with any remaining disagreements being resolved by a third reviewer. Data collection from eligible studies will be conducted according to the data extraction form tested prior to abstraction. Included studies will be examined for quality and bias and will be meta-analysed where applicable. This protocol is reported in keeping with the PRISMA-P guidelines.

Ethics and Dissemination

The results for this review will be disseminated through publications in peer-reviewed journals, posters and presentations at scientific conferences. Additionally, we are collaborating with the Canadian Addiction Treatment Centre (CATC) clinics to help disseminate the findings for this review. As this is a systematic review, no ethics approval is needed.

Systematic Review Registration: CRD42020178441

ARTICLE SUMMARY

Strengths and limitations of this study

Strengths

- To our knowledge, this will be the first systematic review examining the association between vaping and health outcomes in the OUD population.
- We aim to conduct additional analyses examining mortality, overdoses, hospitalizations, and emergency room visits related to vaping.

Limitations

- This review may be limited in the number of articles identified that are investigating vaping and health outcomes in the OUD population.

Key words: systematic review protocol, vaping, opioid use disorder, health outcomes

Manuscript Word Count: 1934

INTRODUCTION

Rationale

Vaping behaviour has increased in popularity, raising many questions about short- and long-term health outcomes in at-risk individuals given the scarcity of evidence and methodological investigations conducted within these populations. Vaping is described as inhaling and exhaling a product which is referred to as a vapor[1]. Vapours are aerosols derived from the heating of a substance, most typically being comprised of nicotine, flavours, and recently, cannabis[2,3]. One of the most commonly known and used vaping devices is the e-cigarette which was initially introduced to the public as being a healthier alternative to smoking a combustible cigarette[4]. However, increasing evidence suggests that e-cigarettes release other toxins such as volatile organic compounds, and carbonyls that are not only dangerous to the individuals vaping, but also have potential for second and thirdhand smoking[5,6].

Vaping has gained traction amongst Canadians as a less harmful alternative to cigarettes[7]. The number of individuals between 16-19 years of age who report having ever vaped increased from 29.3% to 37.0% between 2017 and 2018, with the proportion of individuals having vaped 15 days or more within 30 days rising from 2.1% to 3.6% in the same time[8]. While supporters of vaping might suggest increases can be explained by increased uptake of vaping as a substitution for cigarettes in a long-range attempt to quit smoking, evidence indicates that the upward trend in vaping is observed most strongly among those who identify as "never" or "experimental" smokers[8]. As vaping substances such as nicotine or cannabis maintains their addictive properties, this behavior presents a concern for at-risk populations, including those with opioid use disorder (OUD).

Patients with OUD are at greater risk of polysubstance use, as well as physical and mental health co-morbidities[9,10]. Both cigarette smoking and cannabis use are highly prevalent in this population and it remains important to examine the impact of vaping on these patients. Preliminary results from a study investigating pharmacogenetics of OUD in patients receiving medication assisted treatment (MAT) reported nearly 19.2% of individuals with OUD report use of vaping products, with the majority being men (56%). Nicotine vaping was reported by 74% of participants; 33% reported vaping cannabis (THC, CBD, Marijuana and shatter). 11% reported vaping cannabis and nicotine, and 5.5% reported vaping water or "flavour"[11].

The high prevalence of vaping within this population, in addition to a greater susceptibility toward mental and physical health challenges, necessitates further investigation of the impact of vaping on health outcomes. The primary objective of this study is to systematically review literature pertaining to vaping in patients with OUD in order to extract known health outcomes and identify gaps to inform future studies. We hypothesize that vaping will be associated with negative health outcomes in the OUD population.

Objectives

The objective of this systematic review is to is examine and synthesise the literature investigating the association between vaping and various health outcomes in patients with OUD. Specifically, we aim to:

1. Summarize the literature examining the association between vaping behaviour and health outcomes in patients with OUD (primary outcomes: physical and mental health conditions related to vaping, secondary outcomes: mortality, overdoses, hospitalizations, and emergency room visits related to vaping)
2. If possible, pool studies together to conduct a meta-analysis
3. Conduct sub-group analyses based on age, sex, gender, country, study setting, and type of substance vaped and treatment status of OUD (receiving treatment vs. not receiving treatment)

METHODS AND ANALYSIS

This protocol was reported using the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guideline[12].

Eligibility criteria

The included studies will be randomized control trials (RCT) and observational studies that investigate the association between vaping and health outcomes in the OUD population. We will also include any relevant case studies or case series which will then be qualitatively reported. Studies will be excluded if they are incomplete (e.g., ongoing trials, preliminary reports) or are using animal subjects. In the case of multiple RCT papers published under a single trial registration number, we will include the most recent paper that is relevant to the systematic review. We will exclude review papers, editorials, commentaries and conference proceedings/abstracts.

Studies taking place in community-based settings, and in hospital, including in-patient, out-patient and emergency settings, will be assessed. No restrictions will be made on age, sex, gender, language, country, study population or study design.

Outcomes and prioritization

The primary objective of this systematic review is to identify the health outcomes associated with vaping in patients with OUD. For example, these outcomes may include physical health conditions such as cardiovascular health, pain conditions, respiratory health (including any acute respiratory syndromes' effects) or mental health conditions such as other substance use disorders, depression, and anxiety disorders. The secondary outcomes for this review include mortality, overdoses, emergency room visits and hospitalizations associated with vaping in patients with OUD.

Information sources

For this review, we will be searching all relevant search engines for RCTs and observational studies including: MEDLINE, EMBASE, PsycINFO, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Cochrane Clinical Trials Registry, the National Institutes for Health Clinical Trials Registry and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) from inception until December 31st, 2020. Additionally, to identify related grey literature, we will search thesis dissertations databases and reference lists of included studies will be searched for additional articles and resources.

A health sciences librarian (SS) will be consulted when creating the search strategies for the various databases identified. A broad search strategy will be employed to include titles, abstracts, and keyword fields. The included terms in the search strategy are related to OUD and vaping. We present the search strategy for one of the included databases (Table 1) and will include the complete table of search strategies for all databases in the full review. These databases will be searched from inception to present, without language or demographic constraints, and will be limited to human studies.

Table 1. Search strategy

Database	Search Strategy
MEDLINE	1. exp Opioid-Related Disorders/ 2. exp Heroin Dependence/ 3. exp Substance-Related Disorders/ 4. ((opiate* or opioid* or heroin* or oxyco* or codeine* or dilaudid or fentanyl or drug* or substance*) adj2 (use* or using or misuse* or abus* or dependence* or dependent* or addict*)).ti,ab. 5. exp Vaping/ 6. exp Electronic Nicotine Delivery Systems/ 7. electronic nicotine delivery system* 8. e-cigarette* (truncate) 9. electronic cigarette* 10. vape* (get vapes) 11. vape.mp. 12. vaping.mp. 13. e cigarette.mp. 14. 1 or 2 or 3 or 4 15. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 16. 14 and 15

	limit 16 to humans

Data management

We will use the online platform Covidence to manage references at all stages of the review[13]. Reviewers will be trained on how to use this tool, and this protocol will be shared with all reviewers. Additionally, we will conduct a calibration stage with 50 articles to ensure team members are in agreement for the review criteria.

Selection process

All three stages of the review (title and abstract screening, full text screening, data extraction) will be conducted in duplicate. Any disagreements for inclusion of a study will be resolved through unblinded discussion by these reviewers, with any remaining disagreements being resolved by a third, graduate-level, reviewer. The recommended flow diagram for systematic reviews in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14] will be provided which will list the reasons for inclusion/exclusion. Covidence will be used in all stages of the study selection process including identifying existing duplicates and article organization[13].

Data collection process

The data extraction forms will be created and completed on Covidence and conducted in duplicate. The following items will be collected for each article included for data extraction: author, year, country of origin, population, number of participants (including number of males and females, and number assigned to each group of study), control groups used, and participant demographic details including mean age, and ethnicity. Information on how the authors collected data pertaining to vaping will be noted, including the use of self-report data or validated substance use questionnaires, and type of health outcome reported. For all outcomes, we will also note how they are defined, measured, and the frequency of measurement. If information from an included study is missing, we will contact the authors to obtain that information and keep a log of any correspondence.

Risk of bias in individual studies

All studies included in the data extraction phase will be assessed for risk of bias using appropriate tools corresponding to study design. Such assessments will be completed in duplicate. For RCTs, we will use the Cochrane Risk of Bias Tool[15] and for observational studies, we will use the Newcastle-Ottawa Scale[16]. If possible, on papers that have scored a low risk of bias, we will conduct a sensitivity analysis.

Data synthesis

The identified RCTs and observational studies will be qualitatively reported. If possible, we will conduct meta-analyses for our primary and secondary outcomes, pooling studies with similar study designs and outcome measurements and presenting results using forest plots. We will use a random-effects model which will take between-study and within-study variance into account as opposed to a fixed-effect model to account for expected heterogeneity. We will assess

heterogeneity using the I^2 statistic and 95% confidence interval. We will use the Cochrane recommendation of a I^2 statistic >40% indicating high heterogeneity[17]. Anticipated sources of heterogeneity include age, sex, treatment status, and country, for which we will conduct subgroup analyses. We will also conduct subgroup analyses based on the type of substance that is vaped (i.e. cannabis, nicotine, water flavour). All quantitative analyses will be conducted on RevMan 5.3[18]. Any identified case reports or case series will be qualitatively summarized. If a meta-analysis is not possible (i.e. small number of studies, high heterogeneity), we will present a narrative synthesis of the included papers.

Meta- bias(es)

To address any publication bias, we will conduct an Eggers test if appropriate.

Data Statement

Any additional data can be made available upon request when the review is complete.

Confidence in cumulative evidence

We will utilize the grading of recommendations, assessment, development and evaluation (GRADE) framework to assess the quality of the evidence[19]. This framework will assess the risk of bias, publication bias, consistency, directness and accuracy of the literature.

Patient and Public Involvement

There will be no patient or public involvement for this systematic review.

ETHICS AND DISSEMINATION

The completed systematic review will have a knowledge dissemination component. We will have clinicians, researchers, people that vape as users of this information. We will collaborate with the Canadian Addiction Treatment Centres (CATC), an organization that delivers MAT for the OUD population, to disseminate our findings. We plan to make our findings available to healthcare professionals in various settings through summary reports and resources that will be convenient to access. We will also publish this systematic review in a peer-reviewed journal and present our findings in relevant conferences to the scientific community. No ethics approval is needed as this is a systematic review looking at published literature.

AUTHOR CONTRIBUTIONS

NS and AD: contributed to the conception and design of the study, development of data extraction forms, search strategy, manuscript writing and final review of the manuscript. SS: contributed to the development of the search strategy and final review of the manuscript. TR:

FK: contributed to the critical revision and final review of the manuscript. FK: contributed to the critical revision and final review of the manuscript. CS: contributed to the critical revision and final review of the manuscript. RD: contributed to the critical revision and final review of the manuscript. LT: contributed to the critical revision and final review of the manuscript. ZS: contributed to the conception and design of the study, critical revision and final approval of the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

None.

COMPETING INTERESTS

The authors have no competing interests to declare.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Dr. Samaan is supported by grants from CIHR Awards #156306 and#155404.

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
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	NA
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1 and 7
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	NA
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	7
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	7
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
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	4
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	4
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	5
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Study records - 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)	5

Study records - 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	5
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	6
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
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	6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	6
Data synthesis	#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 I2, Kendall's τ)	6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6