Comparison of various behavioral intervention approaches for tobacco cessation- A protocol for a systematic review and network meta-analysis

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Protocol

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Abstract

Background

Despite substantial progress in tobacco control in the last two decades, there is limited literature on the most effective tobacco cessation behavioral intervention. This network meta-analysis will compare various behavior change intervention for tobacco cessation and attempt to rank them to identify the best approach for cessation.

Methodology

The network meta-analysis will include randomized controlled trials on behavior change for tobacco cessation. The PICOS framework will be used while selecting the studies from various established scientific databases viz. Pubmed, Scopus, Embase, and other sources including Clinicaltrial.gov. The primary outcome for this review will be sustained or point prevalence tobacco abstinence at 6 months or 12 months. To graphically depict and document the studies Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines along with PRISMA Network Meta-Analysis extension statement will be used.

Conclusion

The network meta-analysis will provide the rankings of behavior change interventions thus determining the most and least effective modality for tobacco cessation. The information obtained will be an important guide for policymakers, implementors, and researchers to choose the priority cessation intervention.

Registration

Protocol of this review and network meta-analysis was registered in PROSPERO: International prospective register of systematic reviews (registration number: CRD42020145768).

Background

Despite a 60 million fall of tobacco use burden globally in past two decades, there has been a rise in tobacco use among males by around 40 million.[1] More than 8 million die each year from tobacco use globally including 7 million and 1.2 million from direct and indirect exposure**.** Among smokers, major diseases which are responsible for deaths are vascular, cancer and respiratory diseases[2-5] whereas smokeless tobacco is known to cause cancer of the head, neck, throat, oesophagus and oral cavity as well as various dental diseases. Other than these tobacco consumption elevate the global burden of tuberculosis, and worsens problems like HIV infection and alcohol abuse.[6]

The nicotine, pharmacological active drug present in tobacco, is highly addictive whether taken by inhalation or by ingestion. The absorption of nicotine usually occur through skin, oral mucosa, lungs, or

gut[7] and is the primary constituent component in tobacco that hooks people using it[8]. Besides being highly addictive, it is known to cause serious systematic damage affecting heart, lung, reproductive system, kidney etc. Its rapid onset of action causes immediate effects like irritation, burning sensation in mouth and throat, increase in salivation, vomiting, abdominal pain, nausea, and diarrhoea along with increase in blood pressure, pulse rate and respiration rate resulting in hypothermia,[9] whereas its long term uses causes cell proliferation, oxidation stress, DNA mutation which leads to various cancers.[10]

Substantial progress have been made in the past leading to cost effective and evidence based tobacco control measures. Smoke-free indoor spaces, warnings on the packaging, tax with increase in price and regulation on marketing of tobacco products have been some of the WHO-MPOWER measures which have contributed in some or other way in reducing tobacco use.[11] Despite the fact that 5 billion population from 136 countries have adopted atleast one of the measures at best practice level, the offer help (O) component of MPOWER strategy which has potential to increase the chances of successful quitting and reducing overall burden of tobacco use, is adopted by only 23 countries are protected by this measure. [12] Globally, around 30% of tobacco users have access to cessation service while rest demands for such support eagerly.[13] Around 1.1 billion adult smokers and 367 million smokeless tobacco users[14], have expressed their intention to quit globally.[15,16]

To fullfill the demand of willing people and reduce the burden and prevalence of tobacco users behavioral and pharmacological interventions have been proven to be a boon in different settings.[17,-20] With the wide range of options, easy accessibility, affordability with no side effects behavioral change intervention from health professionals has been cost effective in successfully quitting tobacco use.[21] The behavior change interventions in the form of brief or intensive advice from healthcare professionals during the routine counsulation, toll-free quit lines, text messages, motivational videos or through most handy source i.e., through social media all have been unequivocally proven to be a promising option.

The available literature has documented the effect of solitary behavioral change intervention on quit intention and quitting rate of tobacco users (primarily on smokers) but have not compared or ranked them. Further most of the studies including reviews[22-25] relied upon the history from tobacco users (or their family members) rather than biochemical verification by a standard method, introducing a social desirability bias, resulting in overreporting quitting attempts.[26] The current network meta-analysis will compare multiple interventions simultaneously and analyse studies making different comparison, thus providing evidence on comparative effectiveness of intervention which is valuable for decision making, may not be done by other mean viz. systematic review or meta-analysis.

Objective

The objective of this network meta analysis is to compare and rank the effectiveness of various modalities or their combination which are delivering behavioral interventions for tobacco cessation.

RESEARCH QUESTIONS

- Which is the most clinically effective behavioral change intervention or combination of interventions for tobacco cessation among tobacco users.
- Difference in effectiveness of various behaviour change interventions (or combination of interventions) through different modes among smokeless and smoking form of tobacco users and in different settings.

Methodology

1. Registration

The protocol for this review was registered in Prosper Register of Systematic Review (PROSPERO) database (CRD42020145768). The changes in the protocol while performing the review, if any, will be mentioned in the final report.

2. Study selection strategy

The eligibility criteria for study selection for the review will be done according to the PICOS (Population-Intervention-Comparators-Outcomes-Study design) framework as follows:

I. Study Design

The randomized controlled trials evaluating the impact of different modes of behavioral intervention on tobacco cessation at 6 or 12 months will be included. Multiarm trials will be included whereas crossover trials, quasi-randomized trials will be excluded.

II. Study Participants

Adult tobacco users 18 years or older, giving consent for quitting will be included in for this review. Participants below age 18 and not willing to quit will be excluded from the study. Depending upon the availability of sufficient data we plan to consider the following subgroups analysis: smokers and smokeless tobacco users, visitors of inpatient and outpatient department.

III. Study Interventions

Behavioralinterventions for tobacco cessation delivered via different modalities (such as brief advice, individual, telephone & group counselling, text messages, videos, self-help material and social media application) will be assessed. Besides, the combination treatment involving different modalities together will also be assessed. Though intervention evaluating the effects of pharmacotherapies for tobacco cessation will not be included, however studies evaluating effects of both pharmacotherapy and behavioralinterventions will be included.

IV. Study Comparators

For inclusion in the review, trials comparing behavioral change intervention delivering one of included modalities for tobacco cessation with another, or with a control (e.g. standard care or usual care or no

treatment) will be considered.

V. Study Outcomes

Sustained or point prevalence tobacco abstinence, i.e. 6 months or 12 months with biochemical verification using either exhaled carbon monoxide, urinary, salivary or serum cotinine levels will be the assessment measure for this review and network meta-analysis. Drop outs or loss to follow up participants will be considered as continous tobacco users. Comparison of tobacco abstinence among smoking and smokeless tobacco users and in different settings like out-patient department and in-patient departments will also be involved.

3. Search strategy

The search for the current review will be conducted in the following databases: Pubmed, Scopus, Embase and other sources including Clinicaltrial.gov and will have no date restrictions. Before execution, the research scholar (PD) shall be trained through workshops and independent guidance from experts, in systematic review and network meta-analysis along with subject experts including departments of Community Medicine, Public Health, Psychiatry, Pulmonary Medicine, Cardiology, Otolaryngology, Neurology and Pharmacology whose assistance will also be taken for development of search strategy. Searches will be conducted with experts assistance utilizing different combination of keywords (e.g. behavioral therapy, individual counselling, intensive counselling, telephone counselling, group counselling, messaging, web-based interventions, phone apps, self-help material, audiotapes, videotapes). Search will be done in databases for studies with the English restriction and published in peer-reviewed journals. Besides, manual search from the reference list of relevant studies and contact with authors will be done for obtaining useful information. The unpublished studies in the form of ongoing studies and dissertations will be excluded.

4. Data Collection

Studies identified after using search strategy for selection will be managed in Endnote X8. After duplication removal, titles and abstract of studies will be screened by the research scholar for inclusion. In case of disagreement while screening, the research scholar shall seek advice from adviser/ research guide (SG), for further inclusion in the study. Then both reviewer (PD, SG) will screen the full text of studies for their possible inclusion. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[27] along with PRISMA Network Meta-Analysis extension statement[28] will be used to graphically depict and document the studies satisfying inclusion criteria after screening and excluded studies with the reasons for exclusion.

Data from studies included after screening will be extracted by one reviewer (PD) and verified by co-reviewer (SG). Pre-prepared extraction excel sheet will be used for extraction of data from the included studies for review and analysis. For missing data, authors will be contacted by email for original data. The information extracted from each study will include: study design (duration, follow-up length, country, study sponsor, type of tobacco use), study participants and baseline characteristics (age, gender, sample

size, Fagerstrom Tolerance Nicotine Dependence score, years of tobacco intake and intake per day, any previous quit attempts, any treatment for cessation, tobacco pack years), study intervention and comparison groups (including the behavioral change intervention for tobacco cessation, any mutual intervention), study outcomes of interest will be biochemically verified sustained and point prevalence measures of tobacco cessation for all treatment arms. The arms will be classified with mode of behavioral intervention and the data obtained for the same modality will be pooled together.

5. Data Analysis

Creating geometry of the network

To graphically represent information obtained after pooling data and to provide the available evidence behind each comparison, network diagram will be created. The graphical representation will offer an visual picture of the possible comparisons for modalities when connected in the network. Where nodes will represent different intervention in the network and edges will show the head to head comparison among different modes. The treatment network structure for the review which will be formed after analysis is presented in **(Fig. 1)**.

Network meta-analysis

Network meta-analysis will be performed in Stata 14.2 to synthesize direct as well as indirect evidence for assessing the effectiveness of behavior interventions delivered via different modes. To assess inconsistency between comparisons for loop connecting 3 arms, node splitting method will be used. For presentation of the treatment ranking, P-scores based on the point estimates will be used

Sub group analysis

Subgroup analysis will be used to find the possible sources of significant heterogeneity or inconsistency. It will be performed for population with smoking and smokeless tobacco habit and for different settings.

6. Data synthesis

The quit behavior with various behavioral interventions (along with their different combination) will be summarised in odds ratios. A Frequentist framework will be used to conduct network meta-analysis using Stata 14.2. 95% CIs will be used for reporting all the results. In case of no reports on standard deviations, it will be calculated from available standard errors or confidence intervals. In addition measures, such as surface under the cumulative ranking curve and treatment rankings, will also be reported. After pooling data, we aim analysis to provide comparisons between different modalities of behavioral intervention using pairwise meta-analysis and a view of determining most effective modality in tobacco cessation. For expected significant heterogeneity, random effects model and forest plots will be used to graphically depict the individual and pooled effect sizes.

Assessment of heterogeneity

Studies with similar study design and risk of bias will be used for assessing the methodological diversity. After assuring minimal diversity in the included studies, use of forest plot and I^2 statistics examination will be done to assess the statistical heterogeneity. This will be used in order to provide a visual representation along with the percentage of variability from heterogeneity rather than by chance respectively. In case of heterogeneity with $I^2 > 50\%$ results shall be explored for explanation of differences.

Quality of evidence assessment

Grading of Recommendations Assessment Development and Evaluation (GRADE) framework will be used to assess the quality of evidence in this review. The quality will be assessed at four levels including: high, moderate, low, and very low quality. The starting point of quality for included studies is considered high but may be rated down based on limitations in risk of bias, inconsistency and publication bias.[29,30]

Assessment of risk of bias

Cochrane Risk of Bias Tool (ROB 2)[31] will evaluate the risk of bias for each included study in the review and network meta-analysis. Two reviewers (PD and SG) independently will conduct the assessments, and any disagreement will be resolved via consensus through discussion. In order to obtain additional information for assessment, all the study authors will be contacted. The risk of bias judgement for each domain will be a) Low risk of bias, b) Some concerns or c) High risk of bias. The five bias domains which will be measured includes: 1) Bias arising from the randomisation process, 2) Bias due to deviations from intended interventions, 3) Bias due to missing outcome data, 4) Bias in measurement of the outcome and 5) Bias in selection of the reported result.

Conclusion

Despite with the availability of data reporting impact of pharmacological or in combination with behavioral intervention for tobacco cessation, there is no literature to suggest the ranking of various modality of behavioral interventions, when used alone or in different combinations. The current network meta-analysis aims to address this gap in the literature. The outcomes from the review will help to rank order different modalities and determine the most and least effective treatment for tobacco cessation. The rankings for modalities through network meta-analysis will futher provide evidence for choosing a modality over others. In addition this review will provide understanding of each modality, in the context of tobacco cessation and will directly and indirectly compare all these various behavioral mode of cessation using common comparator. As there is expectation of considerable heterogeneity for included studies, the grouping for comparison shall be done on the modality by which they were delivered. This information obtained will be an important guide for stakeholders, policy makers and researcher to choose a modality on priority basis for delivering an tobacco cessation intervention.

Declarations

Ethics approval and Dissemination

There will be no ethical approval requirement for this evidence synthesis study involving secondary data analysis from RCTs. Dissemination of results from the research will be done to the following groups: the general public, academician, clinicians and healthcare practitioners, policy makers and industries.

Consent for publication & Availability of data and materials

The results of review and network meta-analysis will be publically available through published articles and extracted data will be made available from the corresponding author upon request.

Authors' contribution

The study protocol was planned and designed by PD, SG, AA, AG, DK, RV, RV & BM. While the design for the network diagram was planned by PD & SG. Data extraction and statistical analysis was planned by PD, SG. For provision of critical insight AA, AG, DK, RV, RV & BM was consulted. The first draft of protocol was written by PD and SG, and approved and contributed for the final manuscript by all authors. The PRISMA –P checklist

Consent of participants

As review includes secondary data consent of participants will not be required.

Patient and Public Involvement

Patient and public involvement will not be required for systematic review and network meta-analysis.

Competing interests

The author(s) for the review declares to have no competing interests.

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Figures

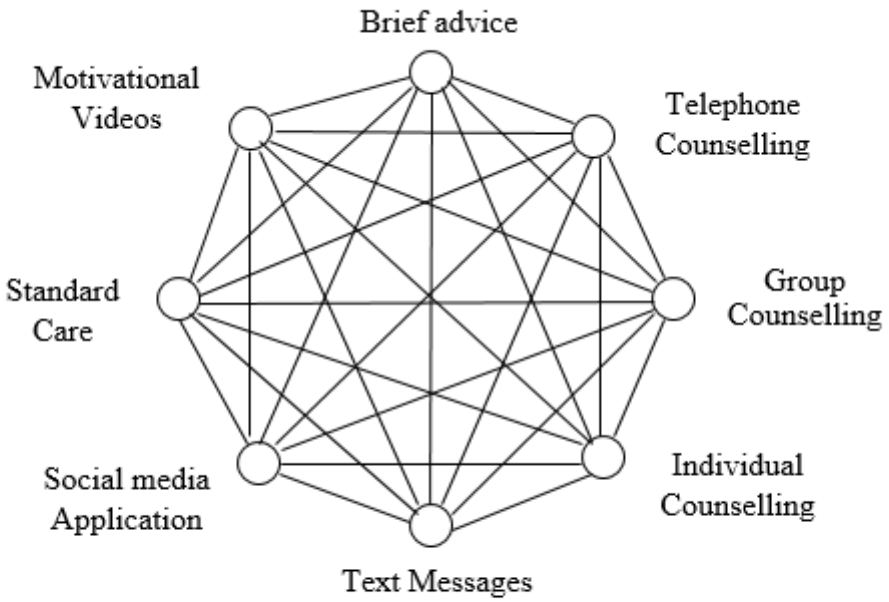

Figure 1: Network structure to show the extent to which the network treatments will be connected and will be dependent upon literature from systematic review and meta-analysis.

Figure 1

Network structure to show extend to which the network treatments will be connected and will be dependent upon literature from systematic review and meta-analysis.

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