Pharmacological intervention on smoking cessation of drinking smokers: a network meta-analysis of randomized controlled trials

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Abstract

Background and Aim: Some clinical trials have reported on the treatment of alcohol-drinking smokers with drugs. This network meta-analysis aims to explore the effect of pharmacological interventions on smoking cessation in such populations. Methods: Only randomized controlled trials (RCTs) were included through a system and comprehensive database search. The risk of bias for the included studies were assessed using Cochrane tool. A network meta-analysis was performed using STATA software to evaluate the effect size between different comparisons, and provide the best smoking cessation intervention based on the SUCRA value. Results: A total of 15 RCTs involving 1565 participants were included. The risk of bias was low in five studies and unclear in ten studies. Network meta-analysis showed that the superiority of quitting smoking was reflected in Varenicline vs Placebo (OR=4.90, 95%CI [1.77,13.55]), Varenicline vs Naltrexone (OR=3.50, 95%CI [1.13,11.06]), and Varenicline vs Bupropion (OR=3.32, 95%CI [1.03,10.74]). None of the other pairwise comparisons showed significant difference. Finally, the probability ranking results indicated that Varenicline was the most effective intervention. Conclusions: The network meta-analysis showed that compared with Naltrexone, Bupropion, and Placebo, Varenicline had obvious superiority in quitting smoking, while there was no difference in effect between other drugs. Meanwhile, we look forward to more high-quality studies to investigate the existing evidence.

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Results: A total of 15 RCTs involving 1565 participants were included. The risk of bias was low in five studies and unclear in ten studies. Network meta-analysis showed that the superiority of quitting smoking was reflected in Varenicline vs Placebo (OR=4.90, 95%CI [1.77,13.55]), Varenicline vs Naltrexone (OR=3.50, 95%CI [1.13,11.06]), and Varenicline vs Bupropion (OR=3.32, 95%CI [1.03,10.74]). None of the other pairwise comparisons showed significant difference. Finally, the probability ranking results indicated that Varenicline was the most effective intervention.

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Keywords: Pharmacotherapies, Smoking cessation, Drinking smokers, Network meta-analysis

What is already known about this subject

· Co-occurring smoking and heavy alcohol use have a high prevalence of comorbidities, and it is a significant public health concern.

· Some drugs are effective for people who are dependent on tobacco or alcohol. However, the current evidence for the effect of pharmacological interventions on drinking smokers is weak.

What this study adds

· For these drinking smokers, Varenicline is superior to other drugs in quitting smoking.

· Overall, the adverse events of the drug and the placebo group are not significantly different, and these drugs are relatively safe.

Introduction

Smoking is one of the main risk factors for many chronic diseases, and it is still the main preventable cause of disease and premature death in the world. It is of great significance to implement smoking cessation treatment for all smokers. Nicotine contained in tobacco products can trigger the release of dopamine and other neurotransmitters in the brain, thereby enhancing smokers' dependence on tobacco. [1] However, smoking is an addictive behavior, for most smokers, it is difficult for them to quit smoking permanently. In a survey of more than 5000 adults in England in 2006, about half of smokers have tried to quit smoking at least once in the past year, and it is estimated that there is a permanent smoking cessation rate of 2% to 3% every year. [2]

For smokers with alcohol problems, they face greater health risks and it is more difficult to quit smoking. Globally, the disability adjusted life years of tobacco and alcohol use rank fourth and fourth and fifth respectively. [3] The co-occurrence of smoking and drinking is a significant public health concern, tobacco use and alcohol use disorder have a high prevalence of comorbidities. Smoking combined with alcohol use has negative health effects, including but not limited to increased cancer risk and mortality. [4-6]Epidemiological studies show that there is a strong positive correlation between smoking and drinking. [3,7] For example, a study published in 2006 investigated cigarette smoking and the risk for alcohol use disorders among adolescent drinkers, and the results showed that smokers had 4.5-fold higher odds of alcohol use disorders than never-smokers. [8] Compared with people who do not drink alcohol, alcoholics have a higher smoking rate. [9-11]For example, Elissa R. et al. conducted a survey in US colleges, and the most obvious finding is that 44-59% of alcoholic drinkers smoke.[12] And clinical trials have shown that drinking after quitting smoking will promote the recurrence of smoking.[13] It can be seen that it may be more difficult for smokers who use alcohol to quit smoking. Therefore, smoking cessation treatment for alcoholics can not only improve the success rate of smoking cessation, but also reduce the cost of medical care.

Drug therapy is the most common way to quit smoking. Randomized controlled trials (RCTs) are widely acknowledged as the design of choice for evaluating the effectiveness of health care. [14,15]Many clinical trials and systematic reviews have revealed the effectiveness of some drugs in smoking cessation. In order to verify the effectiveness of different drugs on alcoholic smokers, a network meta-analysis is conducted in this study. At present, there are some clinical trials on smoking cessation of alcoholic smokers with different drug treatments. The existing traditional systematic review can only compare the effects of experimental drugs and control treatment. The purpose of this network meta-analysis is to directly or indirectly compare the smoking cessation effects of a variety of different drugs on alcoholic smokers, so as to rank the smoking cessation effects of different drugs.

Methods

Search strategy

PubMed, The Cochrane Library, Web of Science, and Embase databases were searched from the date of their inception to August 15, 2021. In addition, supplementary searches were conducted through the WHO International Clinical Trials Registry Platform (ICTRP) search portal and grey literature. The main search strategies were as follows: (smok* OR cigarette OR tobacco OR nicotine) AND (Alcohol* OR drink) AND (cessation OR quit* OR abstinence OR stop*) AND (drug OR medicine OR pharmaco*) AND ("random*" OR "blind*" OR "single-blind*" OR "double-blind*" OR "treble-blind*" OR "triple-blind*").

Inclusion and exclusion criteria

Studies with the following criteria were included:1) Only randomized controlled trials (RCTs) evaluating the effect of different drugs on smoking cessation were included. 2) Population: alcohol-drinking smokers, each trial had reports on consumption of alcohol and smoking. 3) Intervention: the experimental group accepted pharmacotherapies and the control group received a placebo; 3) Outcomes: only the indicators related to smoking were included, smoking cessation rate signified the number of people who quit smoking (such as continuous abstinence and point prevalence abstinence), recorded at the end of each treatment.

Studies that were duplicate reports or with insufficient data, such as protocols, conference proceedings, or abstracts, were excluded. Studies written in languages other than English were not included.

Study selection and data extraction

Two reviewers independently conducted screening and data extraction, with any disagreements resolved by consultation with a third reviewer. After removing duplicate articles, two reviewers screened the titles and abstracts according to the inclusion criteria and then read the full-text articles to determine the final studies for inclusion.

A pre-set standardized form was used to extract the key information by two reviewers, independently. The data that were extracted from each publication included: (1) details of the study, such as the year of publication, study design, name of the first author, and country; (2) characteristics of the population, such as their age and cigarettes smoked per day; (3) details of the intervention, such as the drug name, dose, and duration of treatment; (4) treatment outcomes, including the number of people who successfully quit smoking and any adverse events.

Risk of bias assessment

The risk of bias for the included studies was assessed by two independent reviewers using the Cochrane Collaboration's tool,[16] and disagreements were resolved by consensus or a third reviewer.[17] Seven domains were considered in the evaluation process: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Studies were judged to be "low-risk bias" if all items were "low risk" when one item was unclear risk bias, studies were rated as "unclear risk of bias". When one item was high risk, studies were rated as "high-risk bias". [18]

Data Analysis

Stata 15.1 software (network package and the network graphs package) was used to conduct network meta-analysis. [19,20] A network diagram with nodes and lines was constructed to represent different interventions, the size of the nodes represented the number of populations, and the thickness of lines between the nodes represented the number of studies included. For the quit smoking rate (dichotomous variable), the odds ratio (OR) with 95% confidence interval (CI) was used to estimate the effect size. The network meta-analysis results were summarized base on all possible pairwise comparisons, including mixed comparisons (the combined effect of direct and indirect comparisons) and indirect comparisons.

In addition, a traditional meta-analysis was conducted by RevMan software, Similarly, OR with 95% CI was used to calculate the effect size, and the P -value was used to judge whether there was a statistical difference between interventions. Statistical heterogeneity was assessed with the Chi-squared and I -squared (I^2) tests. High heterogeneity in the results was identified if the tests were statistically significant ($p< 0.05$) and the $I^2 > 50\%$, in which case a random-effects model was selected. Otherwise, a fixed-effects model was used.

The smoking cessation effect of different drugs was estimated based on the surface under the cumulative ranking curve (SUCRA). The value of SUCRA ranged from 0 to 100%, when the SUCRA value was 100%, it indicated that the intervention was the most effective, and the smaller the value, the worse the intervention.

Results

Literature screening process and results

As shown in figure 1, the initial electronic search identified 1025 potentially relevant publications. After the removal of 545 duplicates, the titles and abstracts of 42 relevant publications were screened for eligibility and for full-text review. Finally, a total of 15 RCTs were included. [21-35]

Study characteristics

As shown in Table 1, the included RCTs involved 1565 alcohol-drinking smokers (803 in treatment groups and 762 in control groups). All studies were published between 2005 and 2020 in the United States (n = 13), United Kingdom (n = 1) and Canada (n = 1). Most smokers were over 40 years of age and smoked more than ten cigarettes per day. All studies were the two-arm design and the treatment group in each RCT examined one of six drugs, including Varenicline (n = 5), Naltrexone (n = 4), Topiramate (n = 2), Bupropion (n = 3), and Baclofen (n = 1), meanwhile all RCTs gave a placebo to the control group. The duration of the measurement phase ranged from four weeks to 52 weeks, and the smoking cessation rate was the outcome indicator of all studies, including 7-day point prevalence abstinence, prolonged (continuous) abstinence, and other point prevalence abstinence (direct reports at each stage).

Risk of bias

As shown in Figure 2, Five studies had a low risk of bias. These studies used a random treatment allocation sequence generated by a computer or random number table, allocation concealment with envelopes, and a double-blind execution to ensure the quality of the research design. The remaining ten studies had an unclear risk of bias due to insufficient information in the reports.

Network diagram

As shown in figure 3, a network diagram was conducted based on the six interventions (Baclofen, Bupropion, Naltrexone, Topiramate, Varenicline, and Placebo). A total of five direct comparisons and 10 indirect comparisons were included in this diagram. Varenicline vs placebo occupied a larger proportion, and the placebo group accounted for the largest sample size.

Network meta-analysis

The result of network meta-analysis was shown in figure 4. The final network effect showed that the comparisons with a statistically different including Varenicline vs Placebo (OR=4.90, 95%CI [1.77,13.55]), Varenicline vs Naltrexone (OR=3.50, 95%CI [1.13,11.06]), and Varenicline vs Bupropion (OR=3.32, 95%CI [1.03,10.74]). This signified that compared with placebo, Naltrexone, and Bupropion, Varenicline had an evident superiority in quitting smoking. The comparison between any other interventions did not show a significant difference.

Traditional meta-analysis

As shown in figure 5, six drugs were included. The meta-analysis showed that, compared with the placebo, there was a statistically significant differences in Varenicline (OR= 4.76, 95%CI [1.84, 12.31]). Other drugs did not show a significant superiority in smoking cessation compared to placebo.

Probability ranking

As shown in figure 6, the SUCRA probability ranking showed the different treatment effects of these interventions. For seven interventions, their treatment effects were ranked as follows, Varenicline (SUCRA=85.5), Baclofen (SUCRA=82.9), Bupropion (SUCRA=41.6), Topiramate (SUCRA=41.5), Naltrexone (SUCRA=37.9), and Placebo (SUCRA=10.7).

Safety

As shown in table 2, the adverse events reported in some studies were used to assess the safety of specific drugs. From the results, three drugs (Varenicline, Topiramate, and Bupropion) reported the symptoms and cases of adverse reactions in different groups. These adverse symptoms mainly included nausea, insomnia, headache and depression, etc. From the statistical difference, paresthesia caused by Topiramate, mild nausea caused by Varenicline, and insomnia caused by Bupropion reported more cases than placebo group. For other symptoms, there was no obvious difference between drugs and placebo.

Discussion

Summary of results

In this network meta-analysis, 15 studies covering 1565 patients were included. We evaluated the effectiveness and safety of some drugs (varenicline, naltrexone, baclofen, topiramate and bupropion) in quitting smoking for drinking smokers. The results of network meta-analysis showed that in all 15 pairwise comparisons (including direct and indirect comparison), only Varenicline showed smoking cessation effect compared with Placebo, Naltrexone, and Bupropion, no significant statistical difference was shown in the comparisons between other drugs or placebo. Meanwhile, the results of traditional meta-analysis showed that compared with Placebo, only Varenicline had obvious superiority in quitting smoking. Based on the above analysis, the value of Varenicline for smoking cessation is worth exploring. Judging from the current clinical evidence, many systematic reviews have explored the effect of smoking cessation on Varenicline. However, for the definition of the population, some reviews did not clearly divide it, or focused on other types of populations (such as cardiovascular smokers, schizophrenia smokers, etc.). For example, an updated meta-analysis performed in 2015 by Kishi, T et al. explored the effects of varenicline adjuvant therapy for smoking cessation in people with schizophrenia, [36] the results suggested that although varenicline adjuvant therapy was well tolerated, varenicline was not superior to placebo in smoking cessation. Another systematic review published by Wu, Q et al. determined the effectiveness and safety of varenicline in treating tobacco dependence in patients with severe mental illness, the author pointed out that Varenicline appeared to be significantly more effective than placebo in assisting with smoking cessation. [37] From the conclusions of the above two reviews, the characteristics of the population seem to play an important role in the effect of smoking cessation. Therefore, for drinking smokers, we still need to interpret the existing conclusions carefully.

As for the methodological quality of the included studies, although there are no "high risk of bias " studies, the risk of bias results of more than half of the studies are "unclear risk of bias ", so the methodological quality of these randomized controlled trials is low. Due to the random sequence generation, allocation concealment, and blinding for all people are important design steps of RCT, however, the description information of these three items is unclear, eventually an unclear risk bias is generated. There is no doubt that potential risk bias will reduce the quality of evidence. At the same time, we should consider the impact of other factors on the quality of evidence. For inconsistency, due to no closed loop was formed in the network diagram, thus we did not perform inconsistency test. However, precision, heterogeneity, and publication bias may reduce the level of evidence for some interventions. For example, in network meta-analysis, Varenicline showed statistical differences compared with Placebo, Naltrexone, and Bupropion, but they all had a wide confidence interval (imprecision). Moreover, in traditional meta-analysis, we found high statistical heterogeneity in Topiramate vs Placebo (I^2=69%). Due to few studies, we did not explore publication bias, but we cannot completely ignore the impact of this factor on the level of evidence.

Implications for future research

In this network meta-analysis, we compared different drugs and assessed the level of evidence for different interventions or comparisons. In general, we have made meaningful discoveries. At the same time, in the process of conducting this research, we are still able to provide some implications for future research. First, for drinking smokers, they are a special group of people. Currently, there are a limited number of clinical trials of smoking cessation in such populations, and for some RCTs involving very small sample sizes. Therefore, we look forward to future studies that will focus on such people while also expanding the sample in the trial design to improve the validity of the research evidence. Moreover, following scientific guidance in methodology, the details of the trial design process should be clearly reported. High quality meta-analysis (MA) is increasingly regarded as one of the key tools to obtain evidence, so it is necessary to improve the quality of randomized controlled trials. [38]At the same time, researchers should investigate the potential impact of population variables on outcomes. Because participants' age, degree of tobacco dependence, drug dosage, duration of intervention, and degree of alcoholism may all be important variables that affect smoking outcomes.

Second, the enrichment of intervention methods is an important step to provide the best evidence for clinical decision-making. However, judging from the research published so far, smoking cessation interventions for drinking smokers are mainly some drugs, other non-pharmacological interventions are rarely seen. Moreover,

in these drug trials, it is basically a comparison between one specific drug and placebo. Therefore, future research can explore more intervention models, such as psychotherapy, acupuncture, or non-invasive brain stimulation, etc., which can also be applied to this group of people. At the same time, for pharmacological intervention, more drugs can be considered in one trial to achieve direct comparison between different drugs. Meanwhile we should also actively explore the effect of the combination of these drugs on the outcome of smoking cessation. Finally, the safety and applicability of these drugs should also be fully considered, and timely preventive measures should be taken for inapplicable populations or serious adverse events. Moreover, there should be a detailed record of the usage, dosage, and duration of these drugs.

Limitations

This study has the following limitations: 1) Limited by the search language and authority, we only searched English literature, and may miss some studies that meet the inclusion criteria, which may lead to potential publication bias or language bias. 2) Limited by the search time, new trials may appear in the future, which may lead to changes in the current research results, and we will update it in two years. 3) Different clinical trial studies have different reports on the outcomes of quitting smoking. Some studies use cotinine-confirmed prolonged smoking abstinence, while others use the 7-day point prevalence abstinence. The differences in the reporting methods of quitting smoking outcomes may affect the summary results. Therefore, it is necessary to carefully evaluate the combined effect. 4) A further subgroup analysis was not conducted, we cannot clearly assess the impact of some variables on the current level of evidence. Due to the limited number of studies on specific drugs, we did not analyze the potential effects of age, smoking status, alcohol consumption, drug dosage, duration, etc. on the outcome of smoking cessation.

Conclusion

For drinking smokers, both meta-analysis indicated that Varenicline might be a meaningful drug in quitting smoking, while compared with placebo, the remain drugs do not show obvious superiority in smoking cessation. At the same time, we should comprehensively evaluate the safety of these drugs and seek the best dosage. However, based on the limitations of this study, more large-scale and high-quality randomized controlled trials are needed to provide evidence to support the effectiveness and safety of smoking cessation drugs.

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