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Effects of different pharmacologic smoking cessation treatments on body weight changes and success rates in patients with nicotine dependence: A network meta-analysis

Meng-Tsang Hsieh[1] | Ping-Tao Tseng[2] | Yi-Cheng Wu[3] | Yu-Kang Tu[4,5] | Hung-Chi Wu[6] | Chih-Wei Hsu[7] | Wei-Te Lei[8] | Brendon Stubbs[9,10,11] | Andre F. Carvalho[12,13] | Chih-Sung Liang[14,15] | Ta-Chuan Yeh[16] | Tien-Yu Chen[16,17] | Che-Sheng Chu[18] | Juo-Chi Li[19] | Chia-Ling Yu[20] | Yen-Wen Chen[21] | Dian-Jeng Li[6]

[1] Department of Neurology, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan

[2] WinShine Clinics in Specialty of Psychiatry, Kaohsiung, Taiwan

[3] Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan

[4] Institute of Epidemiology & Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

[5] Department of Dentistry, National Taiwan University Hospital, Taipei, Taiwan

[6] Department of Addiction Science, Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, Kaohsiung, Taiwan

[7] Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

[8] Division of Allergy, Immunology, Rheumatology Disease, Department of Pediatrics, Mackay Memorial Hospital, Hsinchu, Taiwan

[9] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, UK

[10] Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, De Crespigny Park, London, UK

[11] Positive Ageing Research Institute (PARI), Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford, UK

[12] Department of Psychiatry, University of Toronto, Toronto, Canada

[13] Centre for Addiction & Mental Health (CAMH), Toronto, Canada

[14] Department of Psychiatry, Beitou Branch, Tri-Service General Hospital; School of Medicine, National Defense Medical Center, Taipei, Taiwan

[15] Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan

[16] Department of Psychiatry, Tri-Service General Hospital; School of Medicine, National Defense Medical Center, Taipei, Taiwan

[17] Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan

[18] Department of Psychiatry and Center for Geriatric and Gerontology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

[19] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

[20] Department of Pharmacy, Chang Gung Memorial Hospital, Linkou, Taoyuan, Taiwan

[21] Prospect Clinic for Otorhinolaryngology & Neurology, Kaohsiung, Taiwan

Correspondence
Dian-Jeng Li, MD, Department of Addiction Science, Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, No. 130, Kaisyuan 2nd Rd., Lingya Dist., Kaohsiung City 802, Taiwan.
Email: edcrfvm45@gmail.com

Summary

Smoking cessation is a public health priority to reduce smoking-related morbidity and mortality. However, weight gain is a known primary reason for not trying to quit smoking. The aim of the current study was to investigate differences in weight gain associated with different pharmacological smoking cessation interventions. Randomized controlled trials (RCTs) that reported weight gain related to pharmacologic treatments for smoking

Abbreviations: AUC, area under the curve; BW, body weight; CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; ES, effect size; FDA, Food and Drug Administration; ICD, International Classification of Diseases; MD, mean difference; NMA, network meta-analysis; NRT, nicotine replacement therapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized control trial; SUCRA, surface under the cumulative ranking curve

Meng-Tsang Hsieh and Ping-Tao Tseng contributed equally as first authors.

cessation were analysed using network meta-analysis with a random effects model. Thirty-one RCTs with 5650 participants were included. Ten drugs and 22 regimens were identified. Nicotine patches plus fluoxetine, topiramate with/without nicotine patches, nicotine patches plus methylphenidate, nicotine spray/gum/lozenges, high-dose nicotine patches (42 mg/21 mg), naltrexone with/without nicotine patches, or bupropion with/without nicotine patches were associated with less weight gain than the placebo/control arm. Nicotine patches plus fluoxetine were associated with the least weight gain of all smoking cessation treatments. In addition, the nicotine patch plus topiramate and nicotine inhaler was associated with the best success rate and the least dropout rate, respectively. Overall, the nicotine patch 14 mg plus fluoxetine 40 mg, nicotine patch 14 mg plus fluoxetine 20 mg, and topiramate 200 mg would be the three best pharmacologic treatments based upon both weight gain effect and success rate.

KEYWORDS

adverse effect, body weight, network meta-analysis, nicotine dependence, smoke cessation, weight gain

1 | INTRODUCTION

Cigarette smoking increases the burden of cardiovascular disease and is associated with 480 000 deaths every year in the United States.[1] It is a preventable risk factor for ischaemic arterial diseases, and evidence has shown that smoking cessation can decrease the risk of cardiovascular disease and also decrease the associated medical costs.[2] Nicotine antagonist and nicotine replacement therapies (NRTs) are widely used for smoking cessation.

Varenicline, bupropion, and NRT alone or in combination have been shown to improve smoking cessation and also to reduce the cessation failure rate.[3] A network meta-analysis (NMA) in 2014 enrolled 21 randomized control trials (RCTs) on NRTs, 28 on bupropion, and 18 on varenicline,[3] and found that bupropion and varenicline were not associated with serious cardiovascular diseases, but that NRT was associated with an increase in minor cardiovascular diseases (RR, 2.29; 95% CI, 1.39-3.82). This inconsistency may be because smoking cessation itself can decrease the risk of cardiovascular disease, but weight gain, which is common when using NRT to stop smoking, during and after smoking cessation may contribute to the risk of minor cardiovascular diseases.

Nicotine enhances sympathetic tone and increases metabolism, and stopping smoking and the lack of nicotine can decrease metabolism and promote weight gain.[4] Subjects who quit smoking have been reported to have an up to 80% increased likelihood of weight gain,[5] and a 1% to 25% increased likelihood of obesity.[6] In a prospective analysis of three cohort studies in the United States,[7] smoking quitters had a higher risk of diabetes mellitus (22%) than current smokers, and this risk peaked at 2 to 7 years after quitting. In addition, most of the quitters with diabetes mellitus had temporary weight gain after smoking cessation, and the mortality rate of the quitters was similar to that of the current smokers during the same period. In another meta-analysis including 35 cohorts,[8] the subjects who stopped smoking gained 4.10 kg (95% CI, 2.69-3.60) on average. Concerns about weight gain after stopping smoking are a commonly cited barrier to stopping smoking. For example, an observational study found that women were less likely to quit smoking than men because of concerns about weight gain.[9]

Although smoking cessation is a well-known protective factor against cardiovascular diseases, whether or not weight gain after smoking cessation affects the risk of cardiovascular disease is unclear. In most cases, people who quit smoking experience temporary weight gain and have a higher risk of metabolic syndrome.[10] The interaction of smoking cessation and metabolic syndrome in quitters is complex and controversial. In a Korean cohort study, postcessation weight gain did not modify the benefits on coronary heart disease and cardiovascular diseases related to smoking cessation.[11] In addition, compared with those who continued to smoke, those who quit had lower rates of myocardial infarction and stroke. Moreover, for those who quit and gained weight, the reduction in the risk of myocardial infarction was greater than for those who did not gain weight (decrease of 67% for myocardial infarction and 25% for stroke in those who gained weight versus 45% and 25%, respectively, in those who did not gain weight).

Achieving sustained smoke cessation is difficult. Malaise, loss of interest, and poor concentration are common symptoms during cessation.[12] Concern over postcessation weight gain is another issue when quitting smoking. Postcessation weight gain has been linked to difficulty in cessation, delaying the date of cessation, and smoking frequency.[13] It is very important to understand the likelihood of weight change when choosing therapy for smoking cessation. Many RCTs and meta-analyses have reported the benefits of smoking cessation with regards to cardiovascular diseases. However, few head-to-head studies have compared the weight gain effect according to smoke cessation medications. Therefore, the aim of the current NMA was to investigate the potential for weight gain with individual pharmacotherapies, including NRTs, bupropion, varenicline, and other Food and Drug Administration

(FDA)-approved agents for smoking cessation. Also, in order to provide more clear direction for clinicians to choose pharmacologic interventions, we aimed to integrate the evidence of weight gain and the evidence of success rate of smoking abstinence after pharmacologic interventions for nicotine dependence patients.

Key Points

Question: Which pharmacologic smoking cessation interventions are associated with the least body weight gain in patients with nicotine dependence?

Findings: In this network meta-analysis of 31 randomized control trials with 5650 participants, of all pharmacologic treatments, patients with nicotine patches plus fluoxetine/bupropion/topiramate/naltrexone/methylphenidate were associated with less body weight gain than controls. In addition, the nicotine patch plus topiramate was associated with the best success rate; the nicotine inhaler was associated with the least dropout rate. Overall, the nicotine patch 14 mg plus fluoxetine 40 mg, nicotine patch 14 mg plus fluoxetine 20 mg, and topiramate 200 mg would be the three best pharmacologic treatments based upon both weight gain effect and success rate.

Meaning: Nicotine patches plus fluoxetine seemed to be associated with the least body weight gain during smoking abstinence.

2 | METHODS

2.1 | General guidelines applied in the current study

The current NMA followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension guidelines[14] (Table S1). The current study was also registered at PROSPERO (ID: CRD42018112803).

2.2 | Search strategy and selection criteria

We conducted a systematic review of PubMed, ScienceDirect, ClinicalKey, Cochrane Library, ProQuest, Web of Science, Embase, and ClinicalTrials.gov from inception to October 06, 2018 using the following keywords: "(weight gain OR body weight) AND (tobacco OR smoke prevention OR quit smoke OR smoking abstinence OR smoking cessation OR smoke OR nicotine dependence) AND (nicotine replacement therapy OR NRT OR transdermal nicotine patch OR nikodem OR habitual OR nicotine nasal spray OR nicotra OR nicotine gum OR nicorette OR nicotine lozenge OR commit OR nicorette mini lozenge OR sublingual nicotine tablet OR nicoli OR nicorette OR nicotine inhaler OR nicotra OR nicotine partial agonist OR varenicline OR chantix OR cytisine OR tabes OR nicotine antagonist OR bupropion OR zyban OR mecamylamine OR inversion OR nortriptyline OR pamelor OR clonidine OR nicotine vaccine OR nicvax OR nicotine transdermal drug delivery OR nicotine TTS OR Nicotinell)". No language restrictions were applied. We also conducted manual searches for potentially eligible articles from the reference lists of review articles and pairwise meta-analyses.[15,16]

2.3 | Inclusion criteria and exclusion criteria

We only included pharmacologic RCTs, either placebo-controlled or active-controlled, in humans in published articles. Because of the potential heterogeneous sources of the included studies (ie, from psychiatry, surgery, or medicine specialties), we did not set limitations of standard operationalized diagnostic criteria (ie, Diagnostic and Statistical Manual of Mental Disorders [DSM] or International Classification of Diseases [ICD] codes) to diagnose nicotine dependence.

The exclusion criteria included (1) not comparing changes in body weight (BW) before and after pharmacologic treatment, (2) lack of adequate controls, (3) also including antipsychotic management, which would have important impact on BW, (4) comorbid with a diagnosis of other substance dependence, (5) not RCTs, (6) not related to smoking abstinence treatment, or (7) including patients with uncontrolled hypertension, pregnancy, depression, psychiatric disorders, seizures or epilepsy, or alcoholism. In cases of duplicated data (ie, different articles based upon the same sample source), we only included the report with the most informative and largest sample source.

2.4 | Data extraction

Two authors (M.T. Hsieh and P.T. Tseng) independently screened the studies, extracted the relevant data from the manuscripts, and assessed the risk of bias among the included studies. In cases of discrepancy, a third author (D.J. Li) was consulted. If a manuscript lacked eligible data, we contacted the corresponding authors or co-authors to obtain the original data. We followed the flowchart reported in a previous NMA.[17-20] With regards to the dosage of investigated medications, we calculated the average dosage during the whole titration course.

2.5 | Outcomes

The primary outcomes were changes in BW before and after pharmacologic treatment for smoking abstinence. The secondary outcome was the success rate of smoking abstinence and dropout rate by different pharmacologic treatment for smoking abstinence. The definition of success rate was defined as keeping smoking abstinence at the end of study. The definition of dropout was defined as leaving trial before the end of study regardless of any reasons.

2.6 | Cochrane risk of bias tool

Two independent authors (M.T. Hsieh and P.T. Tseng) evaluated the risk of bias (interrater reliability, 0.85) for each domain described in

the Cochrane risk of bias tool.[21] The studies were then further classified into an overall risk of bias category.

2.7 | Statistical analysis

This NMA was performed using STATA version 14.0. For continuous data, we estimated summary mean differences (MDs) with 95% confidence intervals (CIs) (in units of kg). For dichotomous data, we estimated summary odds ratio (OR) with 95% CIs. Because of the presumed heterogeneity among the included studies, with regards to either the sample source or study methods, we used a random effects model in pairwise meta-analysis and frequentist models in the NMA to compare the effect sizes (ESs) between studies with the same interventions. All comparisons were two-tailed, and a *P* value of 0.05 was considered to be statistically significant. Heterogeneity among the included studies was evaluated using the tau value, which was the estimated standard deviation of the treatment effect across the included studies.

With regards to the meta-analysis procedure applied in this study, we used a mixed treatment comparison with generalized linear mixed models to analyse the direct and indirect comparisons in the NMA.[22] Specifically, the indirect comparisons were calculated by transitivity, which indicated that differences between treatment A and B could be calculated from comparisons with third treatment, C. To compare multiple treatment arms, we combined the direct and indirect evidence from the included studies.[23] The direct evidence between two treatment arms (ie, treatment A and treatment B) indicated that there had been a direct comparison between treatment A and treatment B in at least one of the included studies. The indirect evidence between two treatment arms (ie, treatment A and treatment C) indicated that we obtained the ESs between treatment A and C through combining the ESs between treatment A and B and the ESs between treatment B and C if we did not have a direct comparison between treatment A and C in the included studies. For example, in Figure S2A, there was no direct comparison between the nicotine inhaler group and nicotine spray group in the including studies. We therefore obtained indirect evidence between the nicotine inhaler group and nicotine spray group via comparisons with the placebo/control group. In addition, in the figures of network structure, the lines between nodes represented direct comparisons in various trials, and the size of each circle was proportional to the size of the population involved in each specific treatment. The thickness of the lines was proportional to the number of trials connected to the network. We used the mvmeta STATA command in our NMA and self-programmed STATA.[24] We also used the restricted maximum likelihood methods to evaluate between-study variance.[25]

To provide a more relevant clinical application, we calculated the relative ranking probabilities between the treatment effects of all treatments for the target outcomes. In brief, the surface under the cumulative ranking curve (SUCRA) was defined as the percentage of the mean rank of each medication relative to an imaginary intervention that was the best without uncertainty.[26] When the area under the curve (AUC) was larger, the treatment had a higher rank with regards to the weight gain effect.

We conducted meta-regression to assess the relationships between the effect on weight gain with individual treatments and the characteristics of the participants, including age, gender distribution, and baseline body mass index (BMI). To evaluate the effect of potential factors, we selected studies to perform subgroup analysis.

Finally, we evaluated potential inconsistencies between the direct and indirect evidence within the network using the loop-specific approach and local inconsistency using the node-splitting method. Furthermore, we used a design-by-treatment model to evaluate the global inconsistency among the whole NMA.[27]

3 | RESULTS

After the initial screening procedure, 124 articles were considered for full-text review (Figure S1). Of these studies, 93 were excluded for various reasons (see Figure S1 and Table S2 for a summary). Finally, 31 articles were included in the current study (Table S3). The whole geometric distribution of the treatment arms is provided in Figure S2A-C.

3.1 | Characteristics of the included studies

Across the 31 RCTs investigating the effect of pharmacologic treatment on weight changes in patients with nicotine dependence, a total of 5650 participants providing data of BW (mean age of 43.85 years, mean female proportion of 49.38%, and mean BMI = 27.6 kg/m^2) were included at baseline. The participants smoked between 10 and 30 cigarettes per day for on average 0.5 to 3 years. The detailed information of baseline BMI and BW in each RCTs had been addressed in Table S3. Among those RCTs, 15 RCTs did not provided baseline BW, and 19 did not provide baseline BMI. Nicotine dependence was determined according to the Fagerström Test for Nicotine Dependence in most of the studies. Among the 31 RCTs, the duration of NRT (16 RCTs) was 2 to 13 weeks (including 1-6 weeks tapering), including 12-26 weeks for bupropion (four RCTs), 4-27 weeks for naltrexone (five RCTs), 13 weeks for phenylpropanolamine gum (one RCT), 3 weeks for fluoxetine (one RCT), 12 weeks for lorcaserin (one RCT), 11 weeks for methylphenidate (one RCT), 10 weeks for topiramate (one RCT), and 12 weeks for varenicline (one RCT).

3.2 | Primary outcome: Changes in BW before and after pharmacologic treatment for the patients with nicotine dependence

3.2.1 | Overall geometric structure of the whole network

All 31 included articles reported changes in BW with different pharmacologic treatments, including 23 treatment arms as follows:

topiramate 200 mg, nicotine patch 21 mg plus topiramate 200 mg, nicotine patch 14 mg plus fluoxetine 40 mg, nicotine patch 42 mg, nicotine patch 14 mg plus fluoxetine 20 mg, nicotine patch 21 mg plus methylphenidate, nicotine patch 21 mg plus naltrexone 25 mg, nicotine patch 21 mg plus naltrexone 50 mg, nicotine spray, nicotine patch 21 mg plus bupropion 300 mg, phenylpropanolamine gum, bupropion 300 mg, nicotine patch 21 mg plus naltrexone 100 mg, nicotine inhaler, nicotine lozenge, naltrexone 50 mg, nicotine patch 14 mg, nicotine patch 21 mg, varenicline 2 mg, nicotine gum, lorcaserin 20 mg, lorcaserin 10 mg, and placebo/control (Figure S2A and Table S4A).

3.2.2 | Pairwise meta-analysis

In the pairwise meta-analysis, topiramate 200 mg, nicotine spray, nicotine patch 42 mg, nicotine patch 21 mg plus topiramate 200 mg, nicotine patch 21 mg plus bupropion 300 mg, bupropion 300 mg, nicotine gum, and nicotine patch 14 mg treatment were associated with less weight gain than treatment with a placebo/control [MD = −3.13 (95% CI, −4.39 to −1.86); MD = −2.80 (95% CI, −5.03 to −0.57); MD = −2.50 (95% CI, −3.45 to −1.55); MD = −2.09 (95% CI, −3.23 to −0.95); MD = −0.97 (95% CI, −1.40 to −0.54); MD = −1.25 (95% CI, −2.23 to −0.27); MD = −0.61 (95% CI, −1.13 to −0.10); MD = −0.47 (95% CI −0.76 to −0.18), respectively].

3.2.3 | Network meta-analysis

In the NMA, nicotine patch 14 mg plus fluoxetine 40 mg, nicotine patch 14 mg plus fluoxetine 20 mg, topiramate 200 mg, nicotine patch 21 mg plus methylphenidate, nicotine spray, nicotine patch 42 mg, nicotine patch 21 mg plus topiramate 200 mg, nicotine patch 21 mg plus naltrexone 25 mg, nicotine patch 21 mg plus naltrexone 50 mg, nicotine patch 21 mg plus bupropion 300 mg, nicotine lozenge, nicotine patch 21 mg plus naltrexone 100 mg, bupropion 300 mg, naltrexone 50 mg, nicotine gum, and nicotine patch 21 mg treatment were associated with less weight gain than treatment with a placebo/control [MD = −4.87 (95% CI, −7.70 to −2.04); MD = −4.28 (95% CI, −7.02 to −1.54); MD = −3.13 (95% CI, −4.60 to −1.65); MD = −2.96 (95% CI, −4.29 to −1.63); MD = −2.80 (95% CI, −5.16 to −0.44); MD = −2.50 (95% CI, −3.72 to −1.28); MD = −2.09 (95% CI, −3.46 to −0.72); MD = −1.90 (95% CI, −2.74 to −1.06); MD = −1.69 (95% CI, −2.44 to −0.94); MD = −1.23 (95% CI, −2.00 to −0.46); MD = −1.20 (95% CI, −2.39 to −0.02); MD = −1.12 (95% CI, −1.96 to −0.28); MD = −1.04 (95% CI, −1.64 to −0.43); MD = −0.85 (95% CI, −1.70 to −0.01); MD = −0.59 (95% CI, −1.17 to −0.01); MD = −0.56 (95% CI, −1.12 to 0.00), respectively] (Table S4A and Figure 1A).

3.2.4 | Surface under the cumulative ranking curve

We then ranked the changes in BW related to pharmacologic treatment in the patients with nicotine dependence according to SUCRA. In brief, nicotine patch 14 mg plus fluoxetine 40 mg treatment was associated with the least weight gain, followed by nicotine patch 14 mg plus fluoxetine 20 mg. If we focused on monotherapy, topiramate 200 mg treatment alone was associated with the least weight gain. Finally, if we focused on nicotine products only, nicotine spray was associated with the least weight gain (Table S5A). Meta-regression using restricted maximum likelihood estimators was performed to examine the potential effect of age, gender distribution (in the form of female proportion), and mean baseline BMI on BW changes. The results of this meta-regression did not reveal a significant effect on BW changes when using age, gender distribution, or mean baseline BMI as a moderating variable.

3.3 | Secondary outcome: Success rate of smoking abstinence after pharmacologic treatment for the patients with nicotine dependence

3.3.1 | Overall geometric structure of the whole network

All 23 included articles reported success rate of smoking abstinence after different pharmacologic management, including 22 treatment arms as follows: topiramate 200 mg, nicotine patch 21 mg plus topiramate 200 mg, nicotine patch 14 mg plus fluoxetine 40 mg, nicotine patch 42 mg, nicotine patch 14 mg plus fluoxetine 20 mg, nicotine patch 21 mg plus naltrexone 25 mg, nicotine patch 21 mg plus naltrexone 50 mg, nicotine spray, nicotine patch 21 mg plus bupropion 300 mg, phenylpropanolamine gum, bupropion 300 mg, nicotine patch 21 mg plus naltrexone 100 mg, nicotine inhaler, nicotine lozenge, naltrexone 50 mg, nicotine patch 14 mg, nicotine patch 21 mg, varenicline 2 mg, nicotine gum, lorcaserin 20 mg, lorcaserin 10 mg, and placebo/control (Figure S2B and Table S4B).

3.3.2 | Network meta-analysis

In the NMA, nicotine patch 21 mg plus topiramate 200 mg, nicotine patch 21 mg plus bupropion 300 mg, lorcaserin 20 mg, nicotine spray, nicotine patch 21 mg plus naltrexone 100 mg, bupropion 300 mg, and nicotine patch 14 mg were associated with more success rate than treatment with a placebo/control [OR = 10.50 (95% CI, 1.04-105.75); OR = 3.13 (95% CI, 1.59-6.16); OR = 3.01 (95% CI, 1.15-7.91); OR = 3.17 (95% CI, 1.18-8.50); OR = 2.41 (95% CI, 1.13-5.15); OR = 2.09 (95% CI, 1.31-3.34); OR = 1.84 (95% CI, 1.11-3.05), respectively] (Table S4B and Figure 1B).

3.3.3 | Surface under the cumulative ranking curve

We then ranked the success rate related to different pharmacologic management in the patients with nicotine dependence according to SUCRA. In brief, nicotine patch 21 mg plus topiramate 200 mg treatment was associated with the best success rate, followed by topiramate 200 mg, nicotine patch 21 mg plus bupropion 300 mg. If we focused on monotherapy, topiramate 200 mg treatment alone was associated with the best success rate. Finally, if we focused on nicotine products only, nicotine spray was associated with the best success rate (Table S5B). Meta-regression using restricted maximum

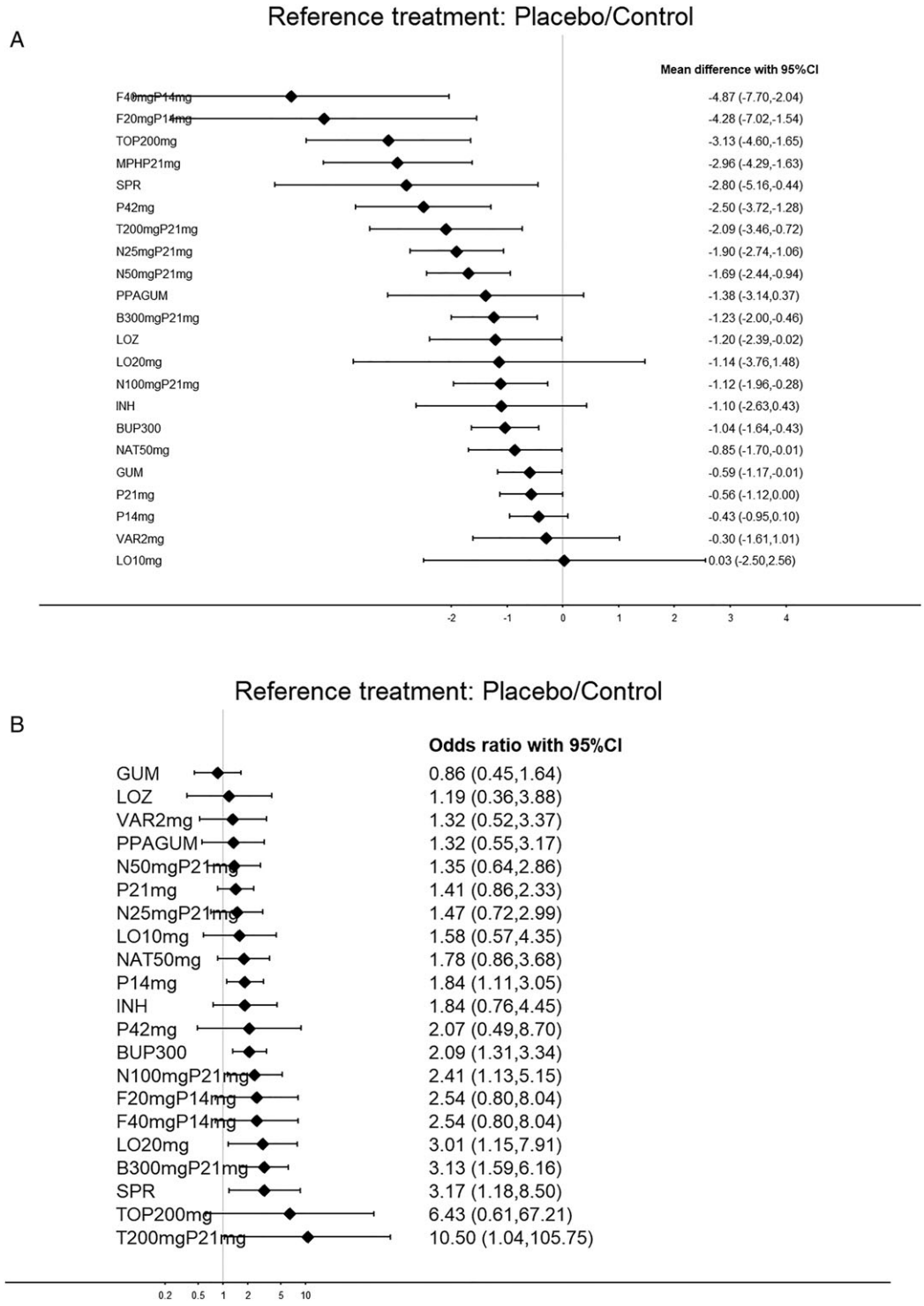

FIGURE 1 Forest plot of the current NMA in reference to placebo/control groups. Figure 1 indicates the forest plot of whole NMA of (A) changes in body weight during smoking abstinence interventions (units: kg), (B) success rate after smoking abstinence interventions, and (C) drop-out rate during smoking abstinence interventions; a mean difference < 0 indicates (A) less body weight gain and a odds ratio < 1 indicated (B) less success rate or (C) less drop-out rate with an intervention than treatment with a placebo/control during smoking abstinence interventions. Abbreviations: B300mgP21mg, nicotine patch 21 mg + bupropion 300 mg; BUP300, bupropion 300 mg; CI, confidence intervals; F20mgP14mg, nicotine patch 14 mg + fluoxetine 20 mg; F40mgP14mg, nicotine patch 14 mg + fluoxetine 40 mg; GUM, nicotine gum; INH, nicotine inhaler; LO10mg, lorcaserin 10mg; LO20mg, lorcaserin 20 mg; LOZ, nicotine lozenge; MPHP21mg, nicotine patch 21 mg + methylphenidate; N100mgP21mg, nicotine patch 21 mg + naltrexone 100 mg; N25mgP21mg, nicotine patch 21 mg + naltrexone 25 mg; N50mgP21mg, nicotine patch 21 mg + naltrexone 50 mg; NAT50mg, naltrexone 50mg; P14mg, nicotine patch 14 mg; P21mg, nicotine patch 21 mg; P42mg, nicotine patch 42 mg; PCo, placebo/control; PPAGUM, phenylpropanolamine gum; SPR, nicotine spray; T200mgP21mg, nicotine patch 21 mg + topiramate 200mg; TOP200mg, topiramate 200 mg; VAR2mg, Varenicline 2 mg

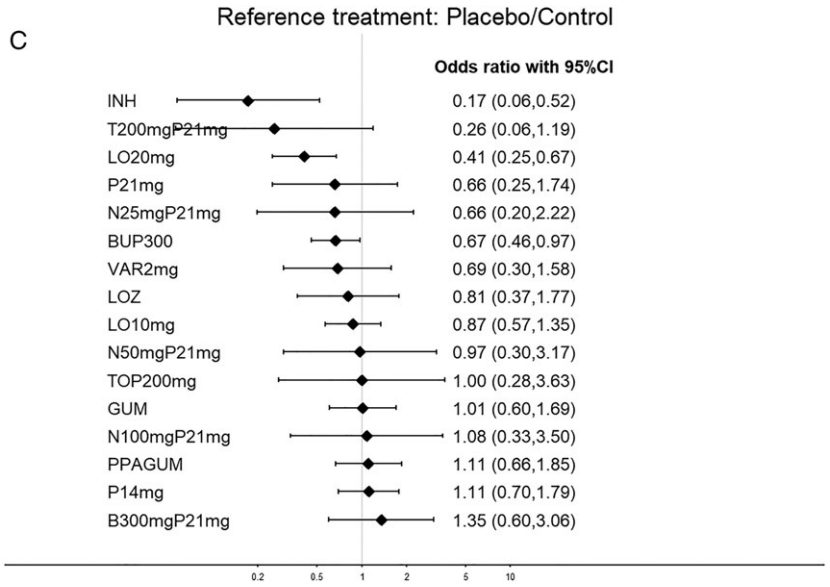

FIGURE 1 (Continued)

likelihood estimators was performed to examine the potential effect of age, gender distribution, and mean baseline BMI on success rate. The results of this meta-regression did not reveal a significant effect on success rate when using age, gender distribution, or mean baseline BMI as a moderating variable.

3.4 | Secondary outcome: Dropout rate of smoking abstinence after pharmacologic treatment for the patients with nicotine dependence

3.4.1 | Overall geometric structure of the whole network

All 11 included articles reported success rate of smoking abstinence after different pharmacologic management, including 17 treatment arms as follows: bupropion 300 mg, varenicline 2 mg, topiramate 200 mg, nicotine lozenge, nicotine gum, nicotine patch 21 mg, nicotine patch 21 mg plus naltrexone 25 mg, nicotine patch 21 mg plus naltrexone 50 mg, nicotine patch 21 mg plus naltrexone 100 mg, nicotine patch 21 mg plus bupropion 300 mg, nicotine patch 14 mg, nicotine patch 21 mg plus topiramate 200 mg, phenylpropanolamine gum, lorcaserin 20 mg, lorcaserin 10 mg, and nicotine inhaler, and placebo/control (Figure S2C and Table S4C).

3.4.2 | Network meta-analysis

In the NMA, nicotine inhaler, lorcaserin 20 mg, and bupropion 300 mg were associated with less dropout rate than treatment with a placebo/control [OR = 0.17 (95% CI, 0.06-0.52); OR = 0.41 (95% CI, 0.25-0.67); OR = 0.67 (95% CI, 0.46-0.97), respectively] (Table S4C and Figure 1C).

3.4.3 | Surface under the cumulative ranking curve

We then ranked the dropout rate related to different pharmacologic management in the patients with nicotine dependence according to SUCRA. In brief, nicotine inhaler was associated with the least dropout rate, followed by nicotine patch 21 mg plus topiramate 200 mg, lorcaserin 20 mg (Table S5C). Meta-regression using restricted maximum likelihood estimators was performed to examine the potential effect of age, gender distribution, and mean baseline BMI on dropout rate. The results of this meta-regression did not reveal a significant effect on dropout rate when using age, gender distribution, or mean baseline BMI as a moderating variable.

3.5 | Risk of bias and publication bias

We found that 63.6%, 31.8%, and 4.6% of the studies had an overall low, unclear, and high risk of bias, respectively. In addition, an unclear risk of bias because of unclear reporting of randomization procedures or blindness was frequently observed (Figures S3A-S3B, available online).

Funnel plots of publication bias across the included studies (Figures S4A-S4F, available online) revealed general symmetry, and the results of Egger's test indicated no significant publication bias among the articles included in the NMA. In general, NMAs do not demonstrate inconsistencies in terms of either local inconsistency as assessed using the loop-specific approach and the node-splitting method, or global inconsistency as assessed using the design-by-treatment method (Tables S7 and S8).

4 | DISCUSSION

The main findings of the current NMA are that nicotine patches plus other medications, and especially fluoxetine, topiramate alone,

bupropion alone, naltrexone alone, nicotine lozenge/gum/spray had superior efficacy in controlling BW with smoking abstinence than placebo treatment. The high-dose nicotine patches (42 mg/21 mg) also had superior efficacy in controlling BW. Among all of the smoking abstinence interventions, nicotine patch 14 mg plus fluoxetine 40 mg treatment was associated with the least weight gain. In addition, the nicotine patch 21 mg plus topiramate 200 mg was associated with the best success rate, and nicotine inhaler was associated with the least dropout rate. If we focused on monotherapy, topiramate 200 mg treatment alone was associated with the best success rate and least weight gain. Finally, if we focused on nicotine products only, nicotine spray was associated with the best success rate and least weight gain. The SUCRA ranking of the weight gain and success rate by the investigating pharmacologic treatments had been drawn in Figure 2. On the basis of Figure 2 and calculation of SUCRAweight × SUCRAsuccess, the nicotine patch 14 mg plus fluoxetine 40 mg, nicotine patch 14 mg plus fluoxetine 20 mg, and topiramate 200 mg would be associated with less weight gain and better success rate among all the pharmacologic treatments.

The most important finding of the current NMA was that the combined treatment group was associated with the least weight gain according to SUCRA. Previous research has suggested that smoking abstinence therapies alone can reduce weight gain after smoking cessation,[28,29] and weight gain has also been reported to be lowest in combined treatment groups.[30] It is possible that combined treatment may have a synergistic effect on BW control compared with monotherapy. In the current NMA, SUCRA demonstrated that nicotine patch 14 mg plus fluoxetine 40 mg treatment was associated with the least weight gain (reduction of 4.87 kg compared with placebo/control). Fluoxetine, a 5-HT reuptake blocker, has been shown to be an effective anorectic agent during the first few months of treatment[31] (all of the pharmacologic mechanisms are summarized in Table S6). A previous study also reported that fluoxetine was the least associated with weight gain among all the antidepressants investigated.[32] Furthermore, several studies reported that the prescription of fluoxetine in patients with obesity was associated with significant reductions in BW.[33,34] Taken together, nicotine patch 14 mg plus fluoxetine 40 mg treatment might be one of the best options for patients with obesity with nicotine dependence.

Another important finding of our NMA was that among the monotherapies for smoking abstinence, topiramate 200 mg treatment alone was associated with the least weight gain. Topiramate, an anticonvulsant prescribed mainly for the treatment of epilepsy and known to induce BW loss,[35,36] has been reported to be capable of diminishing antipsychotic-induced weight gain in schizophrenic patients without aggravating psychotic symptoms.[37,38] In addition, topiramate has also been shown to improve insulin sensitivity, glucose tolerance, and favourably decreased fasting blood glucose, total cholesterol, triglycerides, and high-density lipoprotein-cholesterol levels.[38-41] Another proposed explanation for the BW loss effect of topiramate is through a reduction in visceral fat associated with a decrease in plasma leptin concentrations and increase in plasma adiponectin concentrations, subsequently leading to an improvement in insulin sensitivity.[42] In addition, adverse conditions such as nausea, dyspepsia and diarrhoea may also contribute to BW loss. With regards to the biochemical mechanism, it has also been reported that topiramate may inhibit carbonic anhydrase (CAs, EC 4.2.1.1) enzymes involved in several steps of de novo lipogenesis, both in the mitochondria and cytosol of cells, which can result in BW loss.[43-45] Another study demonstrated that topiramate can stimulate lipoprotein lipase in adipose tissue and skeletal muscles with a resultant increase in thermogenesis.[46,47] Therefore, topiramate alone may also be suggested for patients with obesity with nicotine dependence.

Topiramate is not only beneficial to weight control but also effective in smoking cessation. We found that topiramate 200 mg treatment alone was associated with the best success rate among monotherapy. As a novel therapy for smoking cessations, topiramate had shown its efficacy in a placebo-controlled RCT.[48] It had been reported that topiramate attenuated heart rate increases induced by nicotine and enhance pleasurable feelings, which may be beneficial to smoking cessation.[49] One possible mechanism is the enhancement of dopamine release by topiramate in reward system.[50] Furthermore,

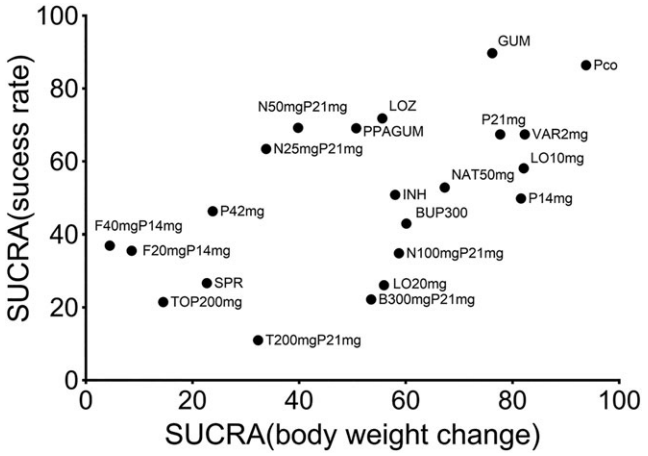

FIGURE 2 The scatter plot of different pharmacologic treatments according to SUCRA ranking of weight gain and success rate. In Figure 2, the *x*-axis indicated the SUCRA of weight gain effect; the *y*-axis indicated the SUCRA of success rate. The less SUCRA, the less weight gain/more success rate was. Therefore, the dot located nearest the zero point would be associated with the least weight gain and best success rate. Abbreviations: B300mgP21mg, nicotine patch 21 mg + bupropion 300 mg; BUP300, bupropion 300 mg; CI, confidence intervals; F20mgP14mg, nicotine patch 14 mg + fluoxetine 20 mg; F40mgP14mg, nicotine patch 14 mg + fluoxetine 40 mg; GUM, nicotine gum; INH, nicotine inhaler; LO10mg, lorcaserin 10 mg; kg, kilogram; LO20mg, lorcaserin 20 mg; LOZ, nicotine lozenge; MPHP21mg, nicotine patch 21 mg + methylphenidate; N100mgP21mg, nicotine patch 21 mg + naltrexone 100 mg; N25mgP21mg, nicotine patch 21 mg + naltrexone 25 mg; N50mgP21mg, nicotine patch 21 mg + naltrexone 50 mg; NAT50mg, naltrexone 50 mg; P14mg, nicotine patch 14 mg; P21mg, nicotine patch 21 mg; P42mg, nicotine patch 42 mg; PCo, placebo/control; PPAGUM, phenylpropanolamine gum; SPR, nicotine spray; SUCRA, surface under the cumulative ranking curve; T200mgP21mg, nicotine patch 21 mg + topiramate 200 mg; TOP200mg, topiramate 200 mg; VAR2mg, varenicline 2 mg

our result demonstrated that nicotine patch 21 mg plus topiramate 200 mg was associated with the best success rate. Previous trial also confirmed that combination therapy (nicotine patch plus bupropion) presented the higher long-term rates of smoking cessation than monotherapy.[30] The current study indicated the superior efficacy of topiramate not only in monotherapy but also in combination therapy. On the other hand, we reported that nicotine spray was the most effective treatment among NRTs. It was similar to a previous meta-analysis, demonstrating that nicotine spray had shown the well-tolerable efficacy for smoking quitting.[51]

Finally, in the current NMA, we also found that the NRT alone was also associated with significantly less weight gain than treatment with a placebo/control. Previous studies have reported that higher dosage NRT products such as nicotine gum appear to reduce weight gain during smoking cessation, and thus they have been recommended as a strategy to prevent undesired weight gain.[52] Furthermore, high-dose nicotine patch therapy is safe and effective to increase short-term tobacco abstinence and to attenuate both short- and long-term postcessation weight gain.[30]

4.1 | Limitations

Several limitations to the current NMA merit further discussion. First, some of the analyses in this study were limited by underpowered statistics, including heterogeneity in the characteristics of the participants (eg, underlying diseases, initial severity of nicotine dependence, and trial duration), the small number of trials for some treatment arms, and the heterogeneous route of medication administration. Second, the methodological quality of the included trials may also have contributed to the outcomes, and this may have limited the interpretation. Third, we did not evaluate the cost-benefit of individual pharmacologic interventions in the current study. Finally, because of the heterogeneity of the included study, we could only provide evidences about difference of weight gain by individual product compared with the others did but not direct evidence about "how much weight gain did one product result in."

5 | CONCLUSION

To the best of our knowledge, this is the first systematic review and NMA to investigate the evidence of potential weight gain with individual pharmacotherapies used as part of smoking cessation interventions. Specifically, treatment with topiramate, bupropion, fluoxetine, naltrexone, and NRT plus other medications had superior efficacy for BW control than treatment with a placebo. Moreover, combined pharmacotherapy was associated with less weight gain than single medications. In addition, the nicotine patch 21 mg plus topiramate 200 mg and nicotine inhaler was associated with the best success rate and the least dropout rate, respectively. Overall, nicotine patch 14 mg plus fluoxetine 40 mg, nicotine patch 14 mg plus fluoxetine 20 mg, and topiramate 200 mg would be the three best pharmacologic treatments based upon both weight gain effect and success rate. Further investigations with a longer period of treatment and other medications are warranted to extend our findings.

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CONFLICTS OF INTEREST

No conflict of interest was declared.

ORCID

Andre F. Carvalho https://orcid.org/0000-0001-5593-2778
Dian-Jeng Li https://orcid.org/0000-0002-6036-045X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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