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Efficacy of Varenicline and Nortriptyline in Smoking Cessation: Indirect Comparison of Randomized Controlled Trials

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Abstract

Varenicline is one of the most effective FDA-approved drugs for smoking cessation, but is unavailable or available by prescription only in many countries. On the other hand, nortriptyline, a common antidepressant, can also be used for smoking cessation. To our knowledge, no head-to-head randomised controlled trial comparing the efficacy of varenicline and nortriptyline exists. Thus, the aim of our meta-analysis study is to determine the efficacy of varenicline versus nortriptyline in smoking cessation using indirect comparison method. In our study, randomized controlled trials which compared varenicline or nortriptyline with placebo were included. MEDLINE and the Cochrane Controlled Trials Register were searched from inception to June 2012. Primary outcome was a 7-day-point prevalence of abstinence at week 12, confirmed by end-expiratory carbon monoxide level < 10 ppm and/or urinary cotinine level < 60 ng/ml. Of the 182 articles identified, 13 studies (n = 6,588) were included in the analysis. Results from direct comparison meta-analysis revealed that both varenicline and nortriptyline was significantly more efficacious for smoking cessation than placebo: varenicline (RR = 2.36; 95% CI 1.98 to 2.82), and nortriptyline (RR = 1.86; 95% CI 1.38 to 2.51). On the other hand, result from indirect comparison revealed no statistically significant difference between varenicline and nortriptyline (OR = 1.61; 95% CI 0.82 to 2.91) with regard to a 7-day-point prevalence abstinence at week 12. This study confirmed the benefit and implied the potential use of nortriptyline in smoking cessation. Nevertheless, a head-to-head comparison of nortriptyline and varenicline on long term continuous abstinence rate should be further examined.

Key word: indirect comparison, nortriptyline, varenicline, smoking cessation

INTRODUCTION

Cigarette smoking remains the leading cause of preventable morbidity and premature mortality worldwide.[1] Benefits of quitting on health are significant.[2] At present, nicotine replacement therapy (NRT), sustained-release bupropion, and varenicline are considered first-line pharmacotherapies for smoking cessation[3] while nortriptyline and clonidine are recommended as second line treatment.[4]

Varenicline is a recently developed partial α4β2 nicotinic acetylcholine agonist. Recent meta-analyses clearly showed that varenicline was significantly more efficacious for smoking cessation than placebo for continuous abstinence at least 6 weeks (OR 2.88; 95% CI 2.40 to 3.47 and RR 2.27; 95% CI 2.02 to 2.55).[5,6] Moreover, varenicline was also found to be superior to single forms of NRT (OR 1.57; 95% CI 1.29 to 1.91), and to bupropion (OR 1.59; 95% CI 1.29 to 1.96).[6] However, according to post-marketing evidences, varenicline may cause depressed mood, agitation, and suicidal behaviour or ideation.[7] In addition, accessibility of varenicline is limited in many

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countries as it has not been approved or it is classified as a prescription drug.

Nortriptyline, a commonly used antidepressant, can also be used for smoking cessation. The advantage of nortriptyline over varenicline is that it is available in most countries worldwide at lower cost. According to a meta-analysis study, nortriptyline was found to be more effective in long term smoking cessation as compared to placebo (OR 2.34; 95% CI 1.61 to 3.41).[8] Its efficacy was also found to be similar to that of nicotine replacement therapy.[8] Furthermore, current evidence clearly indicated that nortriptyline at doses indicated for smoking cessation, is not significantly associated with serious adverse events.[9]

To our knowledge, no direct head-to-head randomised controlled trial comparing the efficacy of varenicline and nortriptyline has been performed. In the absence of direct comparison evidence, indirect comparison is particularly useful.[10-11] The objective of our study is, therefore, to indirectly compare the effects of varenicline versus nortriptyline on smoking cessation, using placebo as a common comparator.

METHODS

Literature search and eligibility criteria

We searched MEDLINE (1966-July 2012), and Cochrane Controlled Trials Register (1985-July 2012) for all randomized controlled trials comparing varenicline (titrated up to 1 mg, twice daily for 12 weeks) or nortriptyline (titrated up to 75-100 mg per day for 12 weeks) with placebo on the 7-day-point prevalence abstinence rate at week 12 confirmed by end-expiratory carbon monoxide (CO) level ≤ 10 ppm and/or urinary cotinine values level ≤ 60 ng/ml. The search strategies were performed by combining the Medical Subject Headings (MeSH) of "Smoking Cessation" and relevant keywords of "varenicline" and "nortriptyline". We also manually searched the reference lists of potentially relevant studies and review articles. Only articles published in English that examining the efficacy of varenicline or nortriptyline among current smokers aged at least 18 years old, who had smoked an average of at least 10 cigarettes per day were included.

Assessment of methodological quality and data extraction

Methodological quality of trails was assessed by two authors (PK and SA) using JADAD score.[12] Only articles with a JADAD score of 3 or higher were included in the meta-analysis. Disagreement was resolved by discussion by MT and UC. Then, PK and SA independently extracted the data using a structured data extraction form. Discrepancies were resolved by discussion with MT. Data was extracted based on intention to treat principle, in which all randomized participants were considered. Authors from some trials were contacted to provide additional data, if necessary.

Statistical analysis

A meta-analysis was conducted using RevMan 5 and WinBUGS 1.4.3 software. Relative Risks (RR) and its associated 95% credible interval (CI) were presented for direct comparison while Odds ratio (OR) and its associated 95% CI was presented for indirect comparison. Random effect model was used whenever there was significant heterogeneity. On the other hand, fixed effect model was used when there was no significant heterogeneity.

RESULTS

Process of study identification was shown in Figure 1. The search of MEDLINE and the Cochrane Controlled Trials Register provided a total of 182 titles. After reviewing all abstracts, duplicated studies and irrelevant studies were excluded. The remaining 25 studies were included to full text review. Thirteen studies[13-25] met eligibility criteria and were included in the review. After searching bibliographies of included studies, no additional study was further included.

Characteristics of all included 13 studies[13-25] were presented in Table 1. After quality assessment, one study comparing varenicline to placebo[17] and one study comparing nortriptyline to placebo[24] were excluded from the meta-analysis.

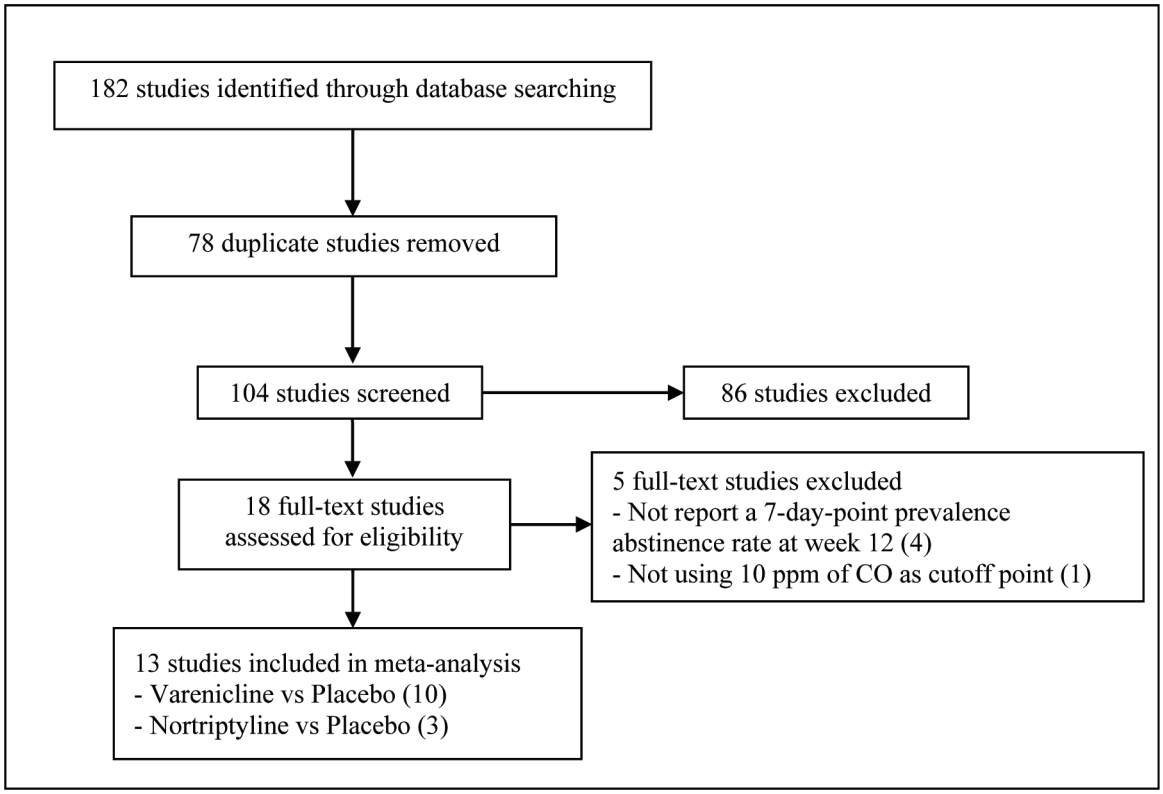

Figure 1. Study identification process

Direct comparison of varenicline with placebo

Our estimate was based on nine trials[13-16,18-22] randomizing 5,815 participants. As a result of significant evidence of heterogeneity ($P < 0.0001$, $I2 = 80\%$), random effect model was employed to combine the results of included studies. Direct comparison between varenicline and placebo revealed that efficacy of varenicline is significantly higher than that of placebo (RR = 2.36; 95% CI 1.98 to 2.82), as shown in Figure 2.

Table 1. characteristics of included studies

Authors/ Years of study	Setting	Participants	Intervention	Outcome measure	JADAD score
Varenicline VS placebo					
Bolliger CT *et al.* / 2008-9[13]	Latin America (Brazil, Colombia, Costa Rica, Mexico, and Venezuela), Africa (Egypt and South Africa), and the Middle East (Jordan, Lebanon, Saudi Arabia, and the United Arab Emirates)	- 588 smokers aged 18-75 years - smoked ≥10 cigarettes/day during the previous 12 months - no cumulative period of abstinence > 3 months in the previous year	varenicline 1 mg bid for 12 weeks	7-day-point prevalence abstinence rate at week 12 and 24 confirmed by expiratory exhaled CO ≤ 10 ppm	5
Gonzales D *et al.*/ 2003-5[14]	USA	- 1,025 smokers aged 18-75 years - smoked ≥ 10 cigarettes per day during the previous 12 months. - fewer than 3 months of smoking abstinence in the past year.	varenicline titrated to 1 mg bid for 12 weeks	7-day-point prevalence abstinence rate at week 12, 24, and 52, confirmed by expiratory exhaled CO ≤ 10 ppm	5
Jorenby DE *et al.*/ 2003-5[15]	USA	- 1,027 smokers aged 18-75 years - smoked ≥ 10 cigarettes per day during the previous 12 months. - fewer than 3 months of smoking abstinence in the past year.	varenicline titrate up to 1 mg bid for 12 weeks	7-day-point prevalence abstinence rate at week 12, 24, and 52, confirmed by expiratory exhaled CO ≤ 10 ppm - continuous abstinence rate at week 9-12, 9-24, and 0-52.	5
Nides M *et al.*/ 2008[16]	USA	- 2,052 smokers aged 18-75 years - smoked ≥10 cigarettes/day during the previous 12 months - no period of abstinence > 3 months in the previous year	varenicline titrate up to 1 mg bid for 12 weeks	7-day-point prevalence abstinence rate at week 12, 24, and 52, confirmed by expiratory exhaled CO ≤ 10 ppm	4
Oncken C *et al.*/ 2006[17]	USA	- 647 smokers aged 18 to 65 years - smoked ≥10 cigarettes per day during the previous year	varenicline titrate up to 1 mg bid for 12 weeks	7-day-point prevalence abstinence rate at week 12, 24, and 52, confirmed by expiratory exhaled CO ≤ 10 ppm	2

Table 1. characteristics of included studies (cont.)

Authors/ Years of study	Setting	Participants	Intervention	Outcome measure	JADAD score
Rennard S *et al.*/ 2008-9[18]	Argentina, Brazil, Canada, China, Czech Republic, France, Germany, Hungary, Italy, Mexico, Republic of Korea, Taiwan, United Kingdom, and United states	- 659 smokers aged 18 - 75 years - smoked ≥10 cigarettes per day during the previous year - fewer than 3 months abstinence during that time, and were motivated to stop smoking.	varenicline titrate up to 1 mg bid for 12 weeks	7-day-point prevalence abstinence rate at week 12 and 24, confirmed by expiratory exhaled CO ≤ 10 ppm	5
Rigotti NA *et al.*/ 2006[19]	Argentina, Australia, Brazil, Canada, Czech Republic, Denmark, France, Germany, Greece, Mexico, Netherlands, Republic of Korea, Taiwan, the United Kingdom, and the United States	-714 smokers aged 35-75 years -smoked an average of ≥ 10 cigarettes daily in the year before enrolment -wanted to stop smoking but had not tried to quit in the past 3 months - had stable, documented CVD (other than hypertension) that had been diagnosed for > 2 months	varenicline titrate up to 1 mg bid for 12 weeks	7-day-point prevalence abstinence rate at week 12, 24, and 52, confirmed by expiratory exhaled CO ≤ 10 ppm	5
Tashkin DP *et al.*/ 2006-9[20]	USA, Spain, France, and Italy	-504 smokers aged more than 35 years -diagnosis of mild to moderate COPD -motivated to stop smoking. -smoked an average of ≥ 10 cigarettes/day over the past year with no period of abstinence > 3 months over that time	varenicline titrate up to 1 mg bid for 12 weeks	7-day-point prevalence abstinence rate at week 12, 24, and 52, confirmed by expiratory exhaled CO ≤ 10 ppm	3
Tsai *et al.*/ 2005-6[21]	Korea, Taiwan	-250 smokers aged 18-75 years -smoked ≥10 cigarettes per day during the past year -no period of abstinence > 3 months in the past year	varenicline titrated to 1 mg bid for 12 weeks	7-day-point prevalence abstinence rate at week 12 and 24, confirmed by expiratory exhaled CO ≤ 10 ppm	5

Table 1. characteristics of included studies (cont.)

Authors/ Years of study	Setting	Participants	Intervention	Outcome measure	JADAD score
Wang C *et al.*/ 2009[22]	China, Singapore, and Thailand	-333 smokers aged 18-75 years -BMI of 15-38 kg/m2 and a weight of at least 45.5 kg - smoked on average ≥ 10 cigarettes per day during the year prior to the screening visit -no period of abstinence ≥ 3 months -were motivated to stop smoking	varenicline titrated to 1 mg bid for 12 weeks	7-day-point prevalence abstinence rate at week 12 and 24, confirmed by expiratory exhaled CO ≤ 10 ppm	3
Nortriptyline VS placebo					
Hall SM *et al.*/ 1998[23]	USA	- 199 smokers aged 21- 65 years - smoked on average ≥ 10 cigarettes per day during the previous year.	nortriptyline titrate up to 50-100 mg/d for 12 weeks	7-day-point prevalence abstinence rate at week 12, 24, 38, and 64, confirmed by expiratory exhaled CO ≤ 10 ppm	4
Hall SM *et al.*/ 2002[24]		220 smokers - smoked on average ≥ 10 abstinence rate at week 12, cigarette per day in the past year	nortriptyline titrate up to 50 to 100 mg/day for 12 weeks	7-day-point prevalence 24, 36, and 52, confirmed by expiratory exhaled CO ≤ 10 ppm and 1 year continuous abstinence rate	2
Wagena *et al.*/ 2002-4[25]	The Netherlands	-255 smokers at risk for COPD or with COPD, aged 30-70 years -had a smoking history of at least 5 years -smoked on average ≥ 10 cigarettes per day during the previous year	nortriptyline titrate up to 75 mg/day for 12 weeks	7-day-point prevalence abstinence rate at week 4, 12, and 26, confirmed by urinary cotinine values of 60 ng/mL or less	5

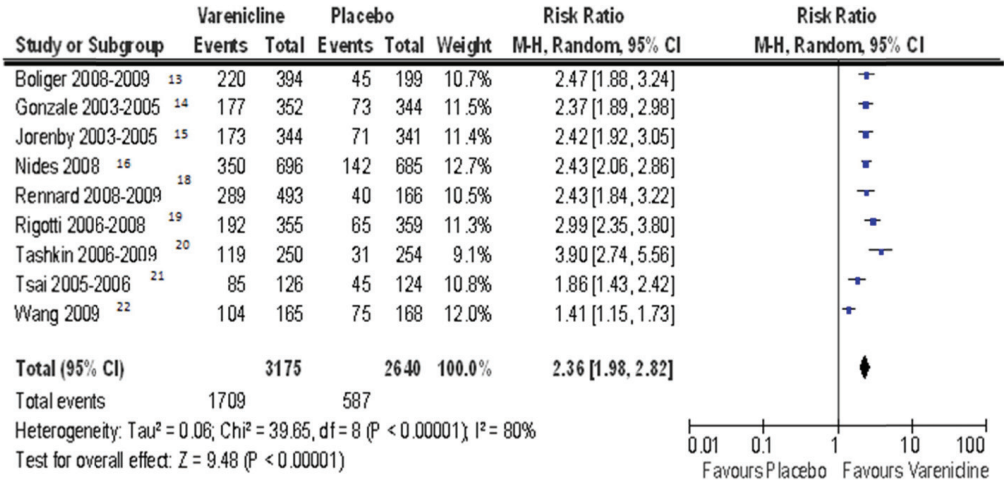

Figure 2. Meta-analysis of randomized controlled trials comparing varenicline with placebo on 7-day-point prevalence abstinence rate at week 12

Direct comparison of nortriptyline with placebo

This analysis was based on two studies[23,25] randomizing 368 participants. There was no evidence of heterogeneity (P = 0.48, I^2 = 0). For this reason, fixed effect model was used to pool the results of included studies. Direct comparison between nortriptyline and placebo indicated that nortriptyline is more efficacious than placebo (RR = 1.86; 95% CI 1.38 to 2.51), as found in figure 3.

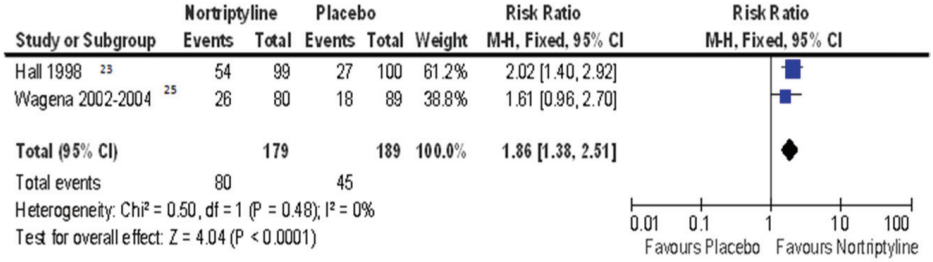

Figure 3. Meta-analysis of randomized controlled trials comparing nortriptyline with placebo on 7-day-point prevalence abstinence rate at week 12

Indirect comparsion of varenicline with nortriptyline

In an absence of direct evidence comparing efficacy between varenicline and nortriptyline, indirect comparison was conducted using WinBUGs software. This estimation was based on 11 studies[13-16,18-22,23,25] randomizing 6,183 participants. Random effect model was used to account for between-study heterogeneity. Result from indirect treatment comparison revealed no significant difference between varenicline and nortriptyline on the 7-day-point prevalence abstinence rate at week 12 (OR = 1.61; 95% CI 0.82 to 2.91).

DISCUSSIONS

This meta-analysis clearly confirmed that efficacy of both varenicline and nortriptyline on smoking cessation was better than placebo. Notwithstanding the limitations of an indirect comparison study, we found no statistically significant difference between varenicline and nortriptyline on a 7-day-point prevalence abstinence rate at week 12. Consider the cost and the accessibility

issues, this study implied the potential use of nortriptyline in smoking cessation especially in the countries where varenicline has not yet been approved. Nevertheless, there are some limitations worthy of being addressed when interpreting our analysis. Firstly, compared with previous meta-analysis,[5,6,8] the result from this study may over-estimate the efficacy of varenicline and nortriptyline, as only short term outcome (7-day-point prevalence at week 12) was assessed. Secondly, although our review was based on comprehensive literature search and included only studies that had high methodological quality, only articles published in English from MEDLINE and the Cochrane Controlled Trials Register were included. As a result, publication bias and database bias might occur. Lastly, although indirect comparison have been advocated when no direct head-to-head comparison is available,[10-11] there was a concern that indirect comparison may be subjected to greater bias than direct comparison.[26] Therefore, we strongly agreed that interpretation of indirect compassion should be made with caution[27] and recommended that head-to-head comparison of varenicline and nortriptyline on long term smoking cessation outcome deserved further investigation.

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