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Varenicline for smoking cessation and reduction in people with severe mental illnesses: systematic review and meta-analysis

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COMPETING INTERESTS

None.

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ABSTRACT

Aims To determine the effectiveness and safety of varenicline in treating tobacco dependence in patients with severe mental illness.

Design A systematic review and meta-analysis of randomised controlled trials that compared varenicline with a placebo or an alternative intervention for smoking cessation or reduction.

Setting Both in-patient and out-patient settings in any country.

Participants Adult patients aged 18 and over with any type of severe mental illness. The systematic review included eight studies comprising 398 participants.

Measures Primary outcome measures were (1) smoking cessation (2) smoking reduction measured by changes in the number of cigarettes smoked per day and (3) number of psychiatric adverse events, which were collected at the end of treatment.

Findings The random-effect pooled estimates from the five studies that reported smoking related outcomes found that varenicline is statistically superior to placebo in smoking cessation (risk ratios 4.33; 95% CI: 1.96-9.56), and smoking reduction was higher in varenicline groups (mean reduced daily cigarettes was 6.39; 95% CI: 2.22-10.56). There is no significant difference regarding neuropsychiatric and other adverse events.

Conclusions Varenicline appears to be significantly more effective than placebo in assisting with smoking cessation and reduction in people with severe mental illness. There appears to be no clear evidence that varenicline was associated with an increased risk of neuropsychiatric or other adverse events compared with placebo.

INTRODUCTION

Smoking is one of the leading causes of preventable mortality, morbidity, and health inequality throughout the world [1]. Smoking prevalence is substantially higher in people with mental disorders, and the likelihood that an individual smokes is positively associated with the severity of the disorder [2,3]. Previous studies have reported that the severe mental illness (SMI) population has a smoking prevalence that is about three times greater than the rate observed in the general population, with estimates ranging from 40% to 88% among people with schizophrenia, and 50% to 70% among those with bipolar disorder [1,4-7]. In this review, SMI is defined as any non-organic disorder with psychotic features that result in a substantial disability, including schizophrenia or other types of schizophrenia-like psychosis (e.g. schizophreniform and schizoaffective disorders), bipolar disorder, or delusional disorder, corresponding to the ICD-10 categories [8].

People with SMI also tend to smoke more heavily than smokers without a diagnosed mental disorder [9-11]. The 2007 US National Health Interview reported a prevalence of heavy smoking (defined as those smoking more than 25 cigarettes a day) of 10.3% among those without a mental disorder, 15.1% in people with bipolar disorder and 17.8% in those with schizophrenia [12].

High levels of nicotine dependence put smokers with SMI at increased risk of smoking-related mortality and morbidity [4,13,14]. A recent study reported that adult smokers with schizophrenia had a 145% higher risk of mortality from smoking-related diseases, such as lung cancer, cardiovascular diseases and chronic obstructive pulmonary disease (COPD), than non-smokers [15]. Smokers diagnosed with bipolar disorder also had a

57% higher risk of smoking-related mortality compared with non-smokers [15]. Given that SMI patients already have a shortened life expectancy, smoking cessation or reduction offers substantial potential benefits [16].

Tobacco use among individuals with SMI is financially costly to both themselves and society due to the cost of treatment of smoking-related diseases. It has been estimated that smokers with SMI spend nearly one-third of their monthly income on cigarettes, thus leaving less available for essentials such as food and housing [17]. The economic burden of smoking-related diseases on society is considerable; in the UK the cost to the NHS of treating smoking-related diseases in the SMI population has been estimated at £719 million per annum [18].

Smokers with severe mental illness are just as likely to want to quit as people without mental disorders [19]. However, due to high levels of tobacco dependence, it is less likely that SMI patients will be successful in their attempts to stop smoking than individuals without mental disorders [1,5,20,21]. Smoking cessation rates in people with schizophrenia are less than half of those reported for smokers in the general population [22]. For many smokers with SMI who cannot quit smoking in the short-term, cutting down their consumption can be a transitional goal before they finally quit. There is evidence to suggest that, while smokers who reduce their cigarettes consumption should be advised to stop smoking, if they are unable to do so in the short-term, reducing the amount that they smoke can be helpful in increasing their likelihood of quitting [23-25]. Meanwhile, these patients will benefit from smoking reduction because they will ingest lower quantities of toxins from smoking cigarettes.

Varenicline is a nicotinic acetylcholine α4β2 receptor partial agonist and an α7 full agonist [2]. As a recent pharmacological treatment, varenicline is expected to provide better effects than existing cessation pharmacotherapies. A recent network meta-analysis, which pooled the results of 12 Cochrane reviews, reported that varenicline significantly increased the odds of smoking cessation in the general population, compared to a placebo (Odds ratio (OR): 2.88, 95% CI 2.40 to 3.47). It is also superior to bupropion (OR: 1.59, 95% CI 1.29 to 1.96) and to any single form of nicotine replacement therapy (NRT; OR 1.57, 95% CI 1.29 to 1.91) in cessation trials [26].

However, safety concerns were raised when clinicians believed that they noted potential association of varenicline with serious neuropsychiatric symptoms in the general population. The U.S. Food and Drug Administration then issued a black box warning for varenicline regarding neuropsychiatric events in 2009 [27]. The adverse neuropsychiatric effects reported in patients taking varenicline include depression, hostility, aggression, psychosis, thoughts of self-harm, suicide and suicidal behaviour, erratic behaviour, and drowsiness.

Because individuals with SMI are often excluded from large-scale studies of smoking cessation and smoking reduction, the available evidence on the use of varenicline in this population is limited. The aim of this review was to review the existing literature on the use of varenicline in patients with SMI for smoking cessation or reduction to determine the safety, tolerance, and efficacy of varenicline for treating tobacco dependence. The primary objectives of this review were: (1) to examine the effectiveness of varenicline compared with a placebo or an alternative intervention on smoking cessation, (2) on smoking reduction, and (3) to assess the risk of psychiatric adverse events of varenicline in people with SMI. This

review extends and updates a previous review of the effectiveness of smoking cessation interventions in people with severe mental illness before the launch of varenicline [28], and reviews of schizophrenia patients only [29,30]. To our knowledge, this is the first systematic review of trial-based studies on varenicline in populations with SMI.

METHOD

Data sources and searches

A systematic review was undertaken, using established methods and following the Cochrane Handbook for Systematic Reviews and the NHS Centre for Reviews and Dissemination (CRD) guidelines [31,32]. We searched MEDLINE, EMBASE, PsycINFO, CINAHL and the Cochrane Library in September 2015. We considered randomised controlled trials (RCTs) without language restriction. We searched the reference lists of identified trials and review articles for additional trials. A bibliographical database, created using EndNote X7, was used to store and manage the retrieved references. An example of the search strategy is given in Appendix 1.

Study selection

Two authors (QW & SP) independently reviewed literature searches to identify relevant trials that met the inclusion criteria. We included both blinded and unblended randomised controlled trials and quasi-randomised controlled trials that compared varenicline to a placebo or an alternative pharmacotherapy, for smoking cessation or reduction in adult patients aged 18 and over with any type of severe mental illness. We included both in-patient and out-patient settings in any country.

Primary Outcomes

The primary outcome measures of interest were (1) smoking cessation in terms of quit rate, (2) smoking reduction measured by changes in the number of cigarettes smoked per day (CPD) at the end of treatment and (3) the safety of varenicline measured by number of psychiatric adverse events in people with SMI.

Data extraction and quality assessment

Two reviewers conducted data extraction independently, using a standardised pre-piloted form. Extracted data consisted of study characteristics, patient characteristics, type of mental illness, varenicline dose, duration of the treatment, length of follow-up, smoking cessation and reduction outcome and also any adverse events recorded alongside the studies.

Studies meeting the inclusion criteria were evaluated by two independent reviewers for their methodological rigour and quality, using quality assessment criteria adapted from the Cochrane risk of bias [31] and Centre for Reviews and Dissemination (CRD) guidance [32]. The modified tool that was developed for the purpose of this review enables the assessment of potential risk of bias, classifying them into three categories (low, high or unclear) depending on six aspects: study design, randomisation, blinding, data collection, confounders and outcome reporting. Any discrepancies were resolved by discussion between reviewers.

Data synthesis and analysis

We conducted meta-analyses following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [33]. For dichotomous outcomes, we summarised the results of each study as a risk ratio (RR). For outcomes measured using continuous variables, such as number of cigarettes smoked per day, the preferred outcome was the difference between the average changes from the baseline. Combined overall effect

sizes were calculated using random effect models. Heterogeneity was quantified by the I2 statistic, where I2 ≥ 50% was considered evidence of substantial heterogeneity [34]. Forest plots were displayed for the meta-analyses, showing individual study effect measures with 95% confidence intervals (CIs), and the overall pooled estimate [35]. Authors were contacted if the results of interest were not reported. For studies that did not report CPD measurements, if expired carbon monoxide (CO) levels were reported, the relevant CO data were converted into cigarette consumption, based on the findings of a previous study [36]. All analyses were conducted with Stata version 13.0 (StataCorp, College Station, Texas). Statistical significance was accepted at $p < 0.05$ in each of the analyses.

RESULTS

Included studies

The search identified a total of 176 relevant studies. Following removal of 64 duplicates, 101 references were excluded based on title and abstract. Full-text assessments of the remaining 11 potentially relevant articles excluded a further three studies [37-39]. A total of eight studies (398 participants) met the selection criteria and were included in the analysis [40-47]. Figure 1 describes the screening process.

The included studies were published between 2011 and 2014. The majority of the trials included patients with schizophrenia or schizoaffective disorder, with only two studies investigating populations with bipolar disorder [40,47]. The trials tended to be small in size (ranging from 5 to 127 participants) compared with smoking cessation trials conducted in the general population [48]. Most were conducted in the United States and none were conducted in the UK. Table 1 summarises the characteristics of the included studies.

The selected randomised trials all compared varenicline with placebo. Three studies explored the effectiveness of varenicline alone, and the remaining studies evaluated varenicline in combination with individual behavioural interventions [42,44,47]. The duration of the varenicline treatment varied between eight and twelve weeks, and 81% of participants treated with varenicline completed the treatment, compared with 82% in placebo groups.

Effectiveness of the interventions

Four trials, with a total of 240 participants, reported smoking abstinence rates after 12 weeks of treatment with varenicline [40,42,45,46]. The pooled results (Figure 2) show that participants using varenicline were more than four times more likely to abstain from smoking at the end of the treatment than the placebo groups (RR 4.33, 95% CI 1.96 to 9.56, $I^2 = 0\%$, p=0.910). The non-significance of the test for heterogeneity suggests that the differences between the studies are explicable by random variation.

In addition, the effectiveness of varenicline was assessed in terms of reduction in CPD (i.e. the number of cigarettes smoked at the end of treatment minus the number smoked at baseline). A random effects meta-analysis of reduction in CPD was performed to estimate the effects of varenicline compared with placebo in terms of smoking reduction. The pooled reduction in smoking at the end of the treatment was significant and favoured varenicline (Figure 3). The weighted mean difference in smoking reduction was 6.39 (95% CI: 2.22-10.56); i.e., smoking was reduced in the varenicline group by 6.39 more cigarettes per day than in the placebo group. But there was substantial heterogeneity among trials ($I^2 = 89.2\%$, $p<0.001$), this is largely due to one trial in which smoking reduction was much higher in the varenicline group than the placebo group [45].

Assessments of psychiatric symptoms and safety

Most of the selected studies reported mental health outcomes and other relevant adverse effects of varenicline in people with severe mental illness. We first examined the outcomes of suicidal ideation, depressed mood, and anxiety, which form the basis for the black box warning on varenicline. Figure 4 shows the pooled relative risk of these neuropsychiatric effects, comparing varenicline to placebo. There were no significant differences between varenicline and placebo in terms of suicidal ideation, depressed mood, or anxiety. However, the numbers of participants in these studies were low, with the largest study having 127 participants. Therefore, these results should be interpreted with caution. Not all of the studies included in this review gave a detailed breakdown of adverse events, and it may be that some adverse events were not reported. It may also be the case that participants who were lost to follow-up experienced an adverse event that was not reported to the study team. Therefore, it is possible that not all adverse events were captured.

Table 2 summarises other adverse effects reported in both the treatment and control groups of the selected studies. The pooled relative risks across studies were reported with corresponding 95% confidence intervals. The most commonly reported adverse effects were nausea, insomnia, abnormal dreams, and fatigue. However, none of the summary estimates showed a significant treatment effect.

DISCUSSION

In this review, a total of eight trials, with 398 eligible participants, published after 2011, were assessed to examine the incremental effect of varenicline, compared with placebo, in people with SMI. The pooled results of the meta-analysis suggest varenicline had a favourable effect

on smoking cessation, compared with placebo in people with SMI (RR 4.33, 95% CI: 1.96-9.56; OR 6.16, 95% CI: 2.47-15.36). In a recent Cochrane systematic review, Cahill and colleagues conducted a meta-analysis of 14 trials and found varenicline was more effective than placebo in smoking cessation for the general population (OR 2.88; 95% CI 2.40 to 3.47) [26]. The increase in the odds of quitting smoking when using varenicline, compared with placebo, is greater for people with SMI than for the general.

With many reviews of smoking cessation interventions, the measurement of quit rates varies amongst the studies. In this review, most studies defined smoking cessation using seven-day point prevalence abstinence at the end of treatment validated by expired CO (i.e. a self-reported 0 cigarettes smoked in the preceding 7 days confirmed by expired CO level of less than 10 ppm). One study defined quit as expired CO level less than 10 ppm at each of the last 4 visits [45], and one study didn't specify how they define smoking cessation [42]. However, none of the studies reported a prolonged abstinence measure (i.e., sustained abstinence for at least six months period) [49]. This suggests the need for assessing prolonged smoking abstinence of smoking cessation interventions in this population.

The primary outcome in this review is smoking cessation at the end of treatment which ranged from 8 to 14 weeks. Follow-up was not clearly reported or achieved in most of the selected studies and only two studies gave results in quit rates at six-month follow-up. In one trial [40], 60% of those who quit after 12 weeks on varenicline had relapsed by the end of six months, compared to 33% of those in the control group. The other study [46] reported a relapse rate of 38% in the varenicline group and a 50% relapse rate in the placebo group at six-month follow-up. This demonstrates that people with SMI who try to quit smoking

relapse easily and more research is needed into relapse prevention interventions for smoking cessation in people with SMI.

In the general population, the standard approach to smoking cessation is to quit abruptly on a designated quit day [50]. However, cutting down on smoking through harm reduction strategies can be an alternative method of managing smoking, given the greater degree of addiction in the SMI population [5,20,21]. Smoking reduction yields substantial benefits by reducing the toxic intake from smoking, reducing the relative risk of smoking-related diseases, and increasing the likelihood of definitively quitting in the future [51].

The results of our meta-analysis suggest that varenicline significantly reduced smoking in people with SMI, compared with placebo. Given that estimates of the rate of quitting vary markedly among studies, in terms of length of time quit, length of follow-up, and means of measurement, the use of changes in daily cigarette consumption as a measurement of smoking behaviour change facilitates direct comparison across studies. Patients in placebo groups reported a reduction in cigarettes per day of 26.9% from baseline, while people treated with varenicline achieved a weighted average CPD reduction of 49.4% from baseline across the studies. Varenicline yielded an additional CPD reduction of 6.39 (95% CI: 2.22-10.56) at the end of treatment, compared with placebo. This indicates that varenicline is an efficacious aid for smoking reduction in people with SMI.

Smokers with severe mental disorders smoke more heavily than the general population [1]. Smokers with SMI included in this review smoked an average of 20.0 (S.D. = 4.9) cigarettes per day with a mean Fagerstrom Test for Nicotine Dependence (FTND) score as high as 5.9 (S.D. = 0.6). The average number of cigarettes smoked per day by adult

smokers was 12.7 in England in 2010 [52]. This indicates that smokers with SMI smoked almost twice as much as those without SMI, and most are heavy smokers (defined as those smoking more than 20 cigarettes a day) [53].

Smoking-related medical illness is the one of the primary causes of morbidity and mortality in SMI patients. Smoking-related comorbidities are associated with higher proportions of heavy smoking [4], and the greater the number of cigarettes smoked daily, the higher the risk of smoking-related diseases and mortality [13,15,54]. Therefore, smoking reduction is expected to generate health benefits for these smokers, even if they are not ready to, or cannot, quit smoking in the short term.

Varenicline is a worthwhile aid to smoking cessation and smoking reduction in people with SMI. However, the safety and risk of neuropsychiatric side effects of varenicline has been debated in literature, thus far without resolution. Some epidemiological studies report an increased risk of adverse psychiatric events associated with varenicline use. For example, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) Yellow Card reports state that varenicline had the highest reported rate of depression disorders, and the second-highest rate of non-fatal suicidal behaviour compared with other drugs in the MHRA study [55]. Similarly, Moore and colleagues studied the FDA's Adverse Event Reporting System (AERS) database from 1998 to September 2010 and found that varenicline substantially increased the risk of reported depression and suicidal/self-injurious behaviour [27].

On the other hand, results from many randomised clinical trials and reviews of trials arrive at a different conclusion. Although higher frequencies of neuropsychiatric side effects have been reported for varenicline in many studies, randomised controlled trials have not shown evidence of an elevated risk when compared with placebo or other smoking cessation

medications [48,56-62]. A recent meta-analysis of 39 randomised controlled trials found no increased risk of suicide or attempted suicide, suicidal ideation, depression, or death in varenicline users when compared with placebo groups in the general population [62]. Amongst the studies included in this review, a majority of studies reported no significant difference between varenicline and control groups in terms of neuropsychiatric events in people with SMIs [40-42,44-45,47]. Only one study reported a significantly increased risk of suicidal ideation in the varenicline group (one case) compared with the placebo group (no cases) [43]. The pooled meta-analysis results show no significant difference in suicidal ideation, depression, and anxiety between varenicline and placebo by the end of the treatment.

Other side effects such as nausea, insomnia, and abnormal dreams were common in both treatment and placebo groups. The overall pooled results showed no significant difference between treatment groups. It is unclear whether some of the adverse reactions to varenicline were partly caused by nicotine withdrawal symptoms. Nicotine in cigarettes is an addictive drug, and nicotine withdrawal produces a wide range of withdrawal symptoms such as headaches, nausea, anxiety, and depression. Previous smoking cessation studies have reported similar symptoms among smokers treated with bupropion, as well as with other nicotine replacement therapies [20,27].

The target population in this review is patients with severe mental illness, namely, patients with schizophrenia or bipolar disorder. For people with psychiatric illnesses, interpretation of neuropsychiatric events may differ from that of the general population. For example, one study reported lifetime suicidal ideation and behaviour rates among recruited patients of 96.8% in the varenicline group and 82.8% in the placebo group [40]. This may

affect the incidence of neuropsychiatric adverse events reported in the trials. However, there is no definitive evidence of the exacerbation of psychiatric symptoms, psychosis, depression or suicidality using varenicline among people with SMI [57,58,64]. The pooled results of this review found no significant difference in neuropsychiatric or other adverse events in people with SMI between varenicline and placebo groups. But the systematic review used only data extracted from RCTs and these may not capture all possible adverse events due to exclusion criteria, i.e. trials only included clinically stable patients. It is important for practitioners to monitor patients closely for neuropsychiatric adverse events during varenicline treatment. Future studies with larger samples are needed to explore the relationship between varenicline and adverse psychiatric events

The Cahill's review found varenicline increased the chances of quitting smoking compared with placebo, single NRT and bupropion in the general population, but there was no significant difference in smoking cessation between varenicline and combination NRT groups [26]. In this review, all eight trials compared varenicline with placebo in treating tobacco dependence in people with SMI. Given that combination NRT and bupropion are recommended by NICE guidance on 'Smoking: acute, maternity and mental health services' and are widely used in prescriptions of stop smoking pharmacotherapies, further studies that compare varenicline with combination NRT and bupropion in people with SMI are recommended [65].

Current varenicline trials in SMI patients tend to use monotherapy, with only a few studies appending behavioural components such as financial incentives or brief advice. There is evidence that, in highly addicted smokers, a combination of treatment such as varenicline combined with bupropion may improve smoking cessation rates. Therefore, such a

combination of treatments is worthy of consideration, given the high level of addiction in patients with SMI [66]. Smokers should be encouraged to use behavioural interventions and pharmacotherapy, since a combination of the two has been proven to be more effective than either intervention alone [67].

Study limitations

To our knowledge, this is the first systematic review of trial-based studies of varenicline in populations with severe mental illness. However, our study has some limitations. First, the included trials tend to be small in size (ranging from 5 to 127 patients). This is because people with severe mental illness are often excluded from large clinical trials, and in those studies that targeted SMI patients, the recruitment rates were normally very low. Second, the follow-up periods in all the studies were short, 8 to 12 weeks in most cases, with only two trials reporting a follow-up assessment at 24 weeks. Third, all eight studies in this review include only clinically stable adult patients diagnosed with SMI. This is a potential source of bias and further research is needed to explore how far findings of this review can be generalised to clinically unstable SMI patients.

CONCLUSION

People with SMI are more likely to smoke and smoke more heavily, than the general population. Smoking harms patients' physical and mental health and increases their financial burden, especially given that many of these patients are in poor physical health and live on government benefits. Smoking-related medical illness is the one of the primary causes of morbidity and mortality in SMI patients; therefore, the development of a safe and effective treatment for smoking dependence is crucial.

In this systematic review, we identified and analysed eight clinical trials that studied the effectiveness of varenicline as an aid to smoking cessation and reduction in people with severe mental illness. The random-effect pooled estimates from the five studies that reported smoking related outcomes showed that, at the end of treatment, varenicline increased the chances of successful smoking cessation four-fold when compared with placebo. The reduction in daily smoking consumption in patients treated with varenicline was significantly greater than in people in the placebo control groups. There was no clear evidence that varenicline was associated with an increased risk of neuropsychiatric or other adverse events in people with severe mental illness, compared with placebo. Future studies with larger sample sizes are needed to provide more evidence of the safety and long-term efficacy of varenicline in smoking cessation and reduction in patients with severe mental illness.

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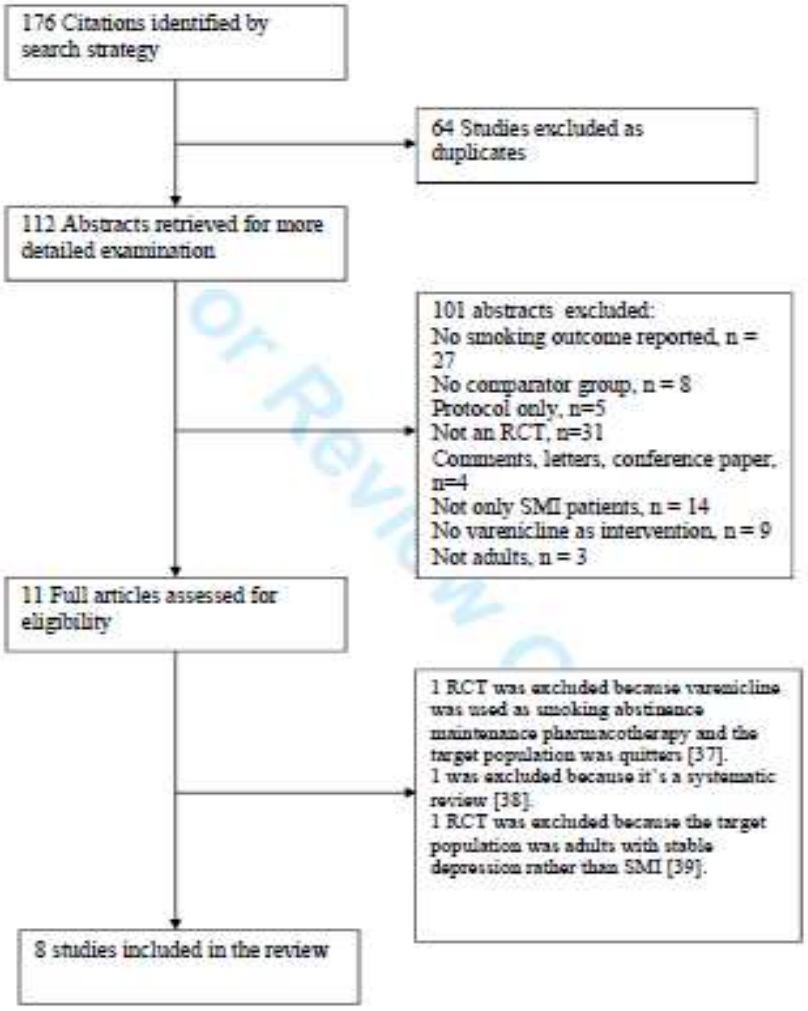

Figure 1 The PRISMA flow chart of included and excluded studies

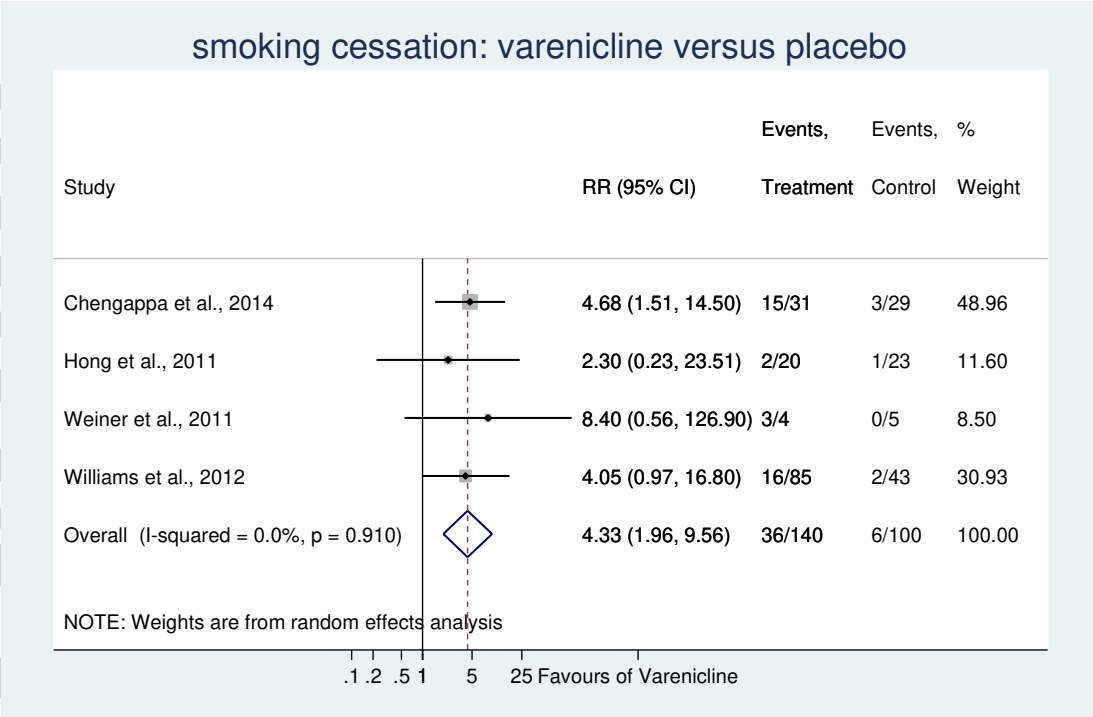

Figure 2 Varenicline versus placebo: smoking cessation at the end of the trial

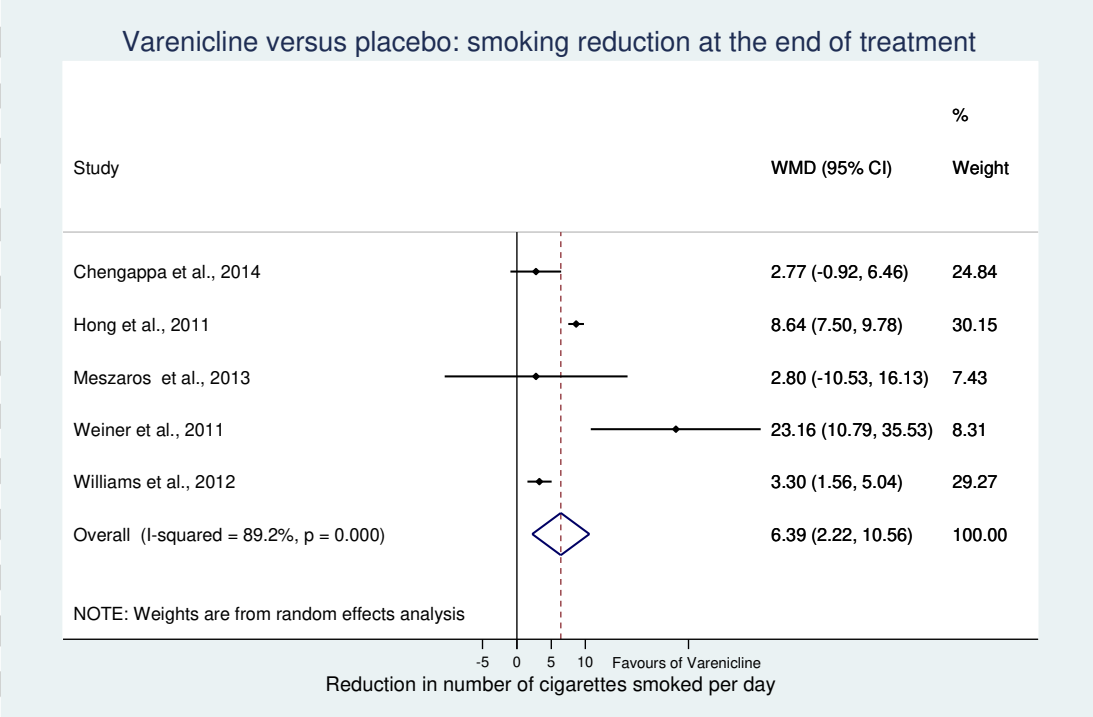

Figure 3 Varenicline versus placebo: smoking reduction at the end of treatment

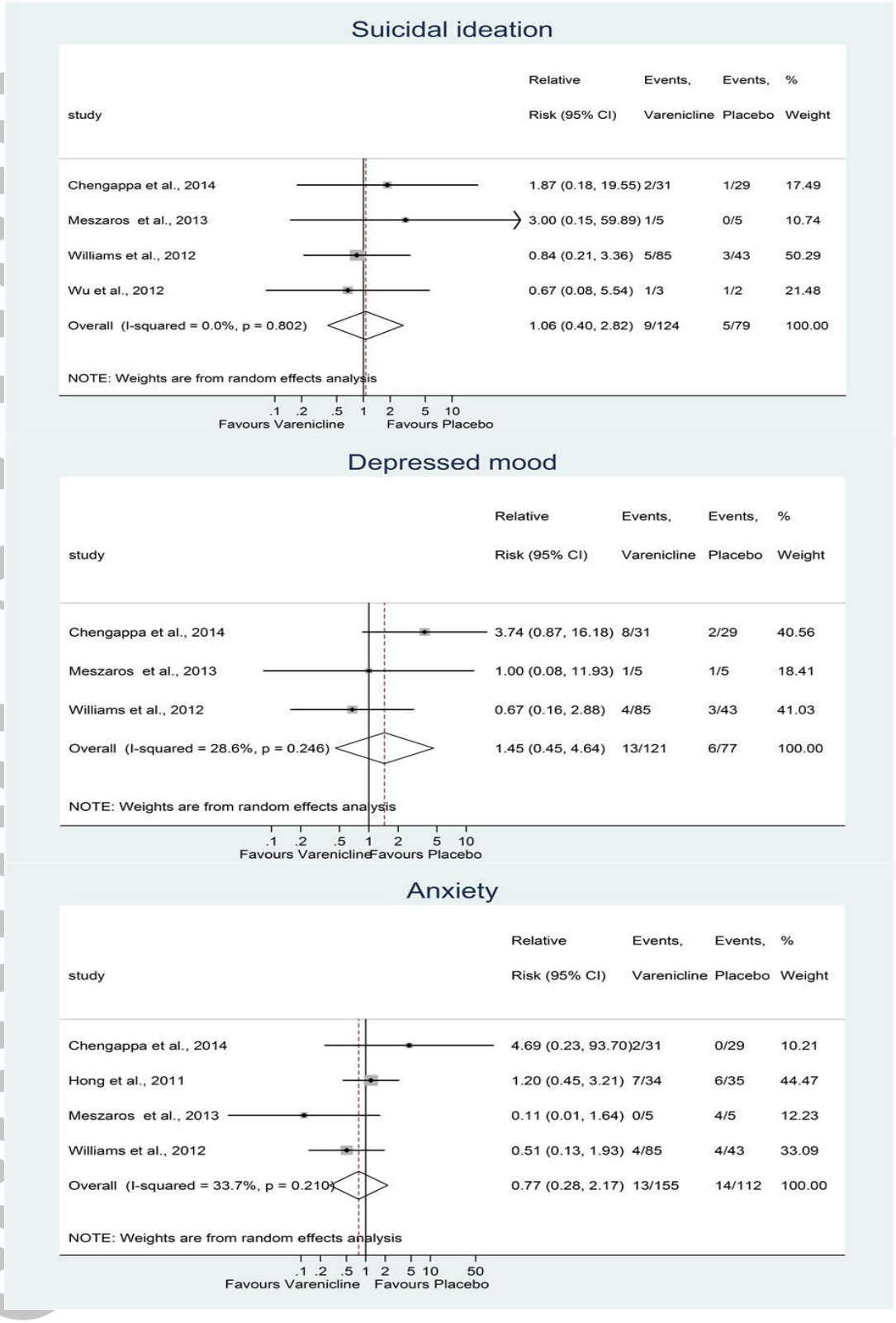

Figure 4 Forest plots: suicidal ideation, depressed mood and anxiety

Table 1 Characteristics of included studies

Authors	Study design and sample	Population	Interventions	Country	Outcome: smoking cessation
Chengappa et al., 2014	RCT, N=60	Clinically stable adult patients aged 18 to 65 with DSM-IV bipolar disorder who smoked at least 10 cigarettes per day. They were willing to quit smoking in the next 30 days and no use of NRT, BUP or nonpharmacologic treatments for smoking cessation in the 3 months prior to the study enrolment.	1. Varenicline tablet of 0.5 mg strength orally at bedtime for day 1-3, increased to 1.0 mg for day 4-7, then 2 mg/day for week 2-12. 2. Placebo for 12 weeks. Both groups received 15 minutes smoking cessation counselling for each visit.	US	7-day point prevalence of sel reported no smoking verified by expired carbon monoxide level < 10 ppm at 12 and 24 weeks.
Fatemi, 2013	RCT, N=24	Clinically stable adults diagnosed with schizophrenia or schizoaffective disorder, who smoked at least 10 cigarettes per day and expressed a motivation to either quit or reduce smoking. Subjects did not use other nicotine products (i.e., smokeless tobacco), and were not currently taking bupropion or varenicline.	1. Varenicline 1 mg twice a day for 12 weeks. 2. Bupropion SR 150 mg twice a day for 12 weeks. 3. Placebo twice a day for 12 weeks. All participants received 20 minutes anti-smoking counselling at each visit.	US	The proposed smoking cessation measure was abstinence as measured by se report and verified biochemically through exhale carbon monoxide (CO), as w as serum and urine levels of nicotine and its metabolite cotinine. However, the result wasn't reported in the paper.
Hong et al., 2011	Double-blind, parallel-groups design, N=69 (N=43 were smokers)	Patients aged 18 to 60 with schizophrenia or schizoaffective disorder, had received antipsychotic medication, and were clinically stable for 4 weeks or longer.	1.Varenicline, 0.5 mg daily for 1 week then 0.5 mg twice daily for 7 weeks. 2. Placebo for 8 weeks.	US	The study reported number o quitters but did not mention how they defined smoking cessation in the methods.
Meszaros et al., 2013	RCT, N=10	Clinically stable outpatients with schizophrenia or schizoaffective disorder and concurrent alcohol and nicotine dependence. Smoked at least 20 cigarettes per day and drank at least 7 standard alcoholic drinks over the 7 days before intake.	1. Varenicline, 0.5 mg daily for day 1 to 3, then 0.5 mg twice daily for day 4 to 7 then 1 mg twice daily for week 2 to 8. 2. Placebo.	US	Not reported.
Shim et al., 2012	RCT, N=120 (60 smokers and 60 non-smokers)	Clinically stable outpatients aged 18 to 60 with chronic schizophrenia. PANSS <=75, CPD > 10.	1.Varenicline 0.5 mg daily for day 1 to 3, then 0.5 mg twice daily for day 4 to 7 then 1 mg twice daily for week 2 to 8. 2. Placebo for 8 weeks.	Korea	No smokers in either treatme group quit smoking entirely.
Weiner et al., 2011	RCT, N=9	Stable schizophrenia or schizoaffective disorder outpatients. Regular smokers (CPD >=10, smoking at least one year and FTND >=4).	1. Varenicline 1 mg twice daily for 12 weeks. 2. Placebo for 12 weeks. Both groups received individual smoking cessation counselling.	US	Smoking cessation (defined a expired CO<10 ppm at each the last 4 visits at week 12. Change in CO from baseline end of study and changes in positive symptoms.
Williams et al., 2012	RCT, N=127	Clinically stable schizophrenia or schizoaffective disorder outpatients (PANSS<70) aged 18-75 years who smoked at least 15 cigarettes per day, and willing to quit in 30 days.	1. Varenicline 0.5 mg tablet for day 1-3, increased to 1.0 mg for day 4-7, then 2 mg/day for weeks 2-12. 2. Placebo. All patients received weekly clinic visits which included smoking cessation counselling.	US and Canada	7-day abstinence at week-12 and week-24 validated by carbon CO.
Wu et al., 2012	RCT, N=5	Clinically stable adult outpatients with a SCID-derived DSM-IV diagnosis of bipolar I or II disorder, who smoked at least 10 cigarettes per day.	1. Varenicline (1 mg twice a day) for 10 weeks. 2. Placebo for 10 weeks. All patients received weekly smoking cessation counselling.	US	Biochemically verified smoking abstinence at trial endpoint by expired breath carbon monoxide levels (<= ppm). Reduction measured b changes in cigar per day. But all of the participants in the control group dropped out at week 3.

Table 2 Adverse effects of varenicline in people with SMI

	Varenicline	Placebo	Pooled Relative Risk	95% CI
Adverse Event	(n=158)	(n=114)		
Gastrointestinal disorders				
Diarrhoea	9	5	1.12	(0.36-3.52)
Constipation	12	13	0.90	(0.43-1.85)
Dry mouth	20	15	1.27	(0.66-2.46)
Flatulence	20	22	0.88	(0.54-1.44)
Vomiting	17	11	1.12	(0.36-3.45)
Nausea	46	25	1.35	(0.89-2.06)
Dyspepsia (heartburn)	10	11	0.89	(0.41-1.95)
Abdominal pain	25	18	1.16	(0.56-2.4)
Gastroesophageal reflux	7	2	3.27	(0.74-14.49)
Psychiatric disorders				
Depressed mood	13	6	1.45	(0.45-4.64)
Anxiety	13	14	0.77	(0.28-2.17)
Suicidal ideation	9	5	1.06	(0.4-2.82)
Mood swings	2	1	1.87	(0.17-19.55)
Insomnia	31	21	1.25	(0.74-2.11)
Abnormal dreams	27	24	0.79	(0.24-2.65)
Nightmare	7	8	0.87	(0.35-2.14)
Euphoria	4	10	0.40	(0.14-1.14)
Hypertension	1	2	0.50	(0.06-3.91)
Nervous system disorders				
Somnolence	16	11	1.43	(0.77-2.67)
Headache	23	30	0.62	(0.36-1.08)
Dizziness	10	9	1.08	(0.48-2.39)
Bad taste	4	2	1.87	(0.37-9.46)
Musculoskeletal/connective tissue disorders				
Artralgia/pain	5	5	0.65	(0.2-2.17)
General disorders				
Fatigue/lethargy	26	17	1.35	(0.8-2.27)
Asthenia/weakness	1	4	0.23	(0.03-1.97)
Irritability	7	6	0.75	(0.29-1.92)
Respiratory disorders				
Rhinorrhea/runny nose	6	6	0.94	(0.34-2.57)
Shortness of breath	4	1	3.74	(0.44-31.55)
Skin manifestations				
Rash	3	2	1.40	(0.25-7.81)
Metabolism and nutrition				
Increased appetite	17	12	1.37	(0.72-2.64)
Decreased appetite	16	15	0.96	(0.51-1.82)
Weight gain	2	2	0.94	(0.14-6.21)
Weight loss	2	1	1.87	(0.18-19.55)
Renal and urinary disorder				
Urinary tract infection	2	0	4.69	(0.23-93.7)
Infections and infestations				
Upper respiratory tract infection	6	1	3.07	(0.38-24.7)