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Outcomes of Transdermal Nicotine Patches Aiding Smoking Cessation among Schizophrenia Patients- A Systematic Review and Meta-Analysis

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Abstract

Background: Prevalence of smoking among schizophrenia patients is very high in the rate of 58%-88%. Previous literature evidence have stated that effect of transdermal nicotine patches and usage of NRT in conjugation with the pharmacotherapy's such as bupropion & varenicline to have a better rate of smoking cessation /and reducing nicotine dependence among schizophrenic population. To have a better understanding on which among these would be an appropriate therapeutic measures in smoking cessation /and reducing nicotine dependence among this population, we systematically analyzed the available literature as it would form the highest level of evidence.

Aim: The aim of this systematic review is to summarize existing evidence for transdermal nicotine patches and pharmacotherapy in smoking cessation among individuals with schizophrenia.

Selection criteria: The review included studies from 2007-2017. Only placebo controlled, Randomized control trials involving human population were considered.

Data Collection and analysis: The titles and abstracts were independently screened by two authors and identified by the search and decided on the possible reports to be included. We obtained and examined full text reports of all potentially relevant trials, to decide whether the studies fulfilled the inclusion criteria.

Main results: Twenty relevant articles were identified (pubmed=12, google scholar=7 trip database=1)'.Thirteen articles were eliminated after reading the title. One article was eliminated due to duplication. Six articles were selected for the abstract reading. After the abstract reading one article was included and three were excluded. Four studies which met the inclusion criteria were taken for the present systematic review. Based on the study findings, it could be stated that the combination of Transdermal nicotine patches and sustained release of bupropion (BUP) was well tolerated, and superior to Transdermal nicotine patches and placebo for short term smoking cessation in schizophrenia.

Conclusion: This systematic review highlights the importance of combination of transdermal nicotine patches and Bupropion in increasing smoking abstinence rates among smokers with schizophrenia.

Introduction

Schizophrenia is a universal disease; with an overall prevalence of 1.1% of the total world population over the age of 18 years which equals to as many as 51 million people worldwide suffering from schizophrenia[1].In India, prevalence of schizophrenia is approximately 1.4 % among 18-65 year old population[1]. Medical morbidity and mortality rates remains elevated in schizophrenia patients compared to the general population, in part due to potentially irreversible medical risk factors.

Literature review shows patient with schizophrenia have higher rates of smoking than in general population and are more refractory to smoking cessation. In addition, smokers with schizophrenia smoke more heavily and extract more nicotine from each cigarette [2, 3].This has been suggested as a major contributing factor to higher morbidity ranging from malignancy, cardiovascular and respiratory diseases, obesity, diabetes, and hypertriglyceridemia in this group of patients, especially in people aged 35 to54 years[4, 5].Interventions that have reduced medical morbidity in the general population can be adopted to reduce premature mortality in individuals with schizophrenia.

Chronic nicotine use among schizophrenic population has been documented to increase dopaminergic neurotransmission; especially in the prefrontal cortex reducing prefrontal activity by nicotine which could alleviate the symptoms of schizophrenic patients**.** The resulting symptomatic relief could motivate patients with schizophrenia to continue smoking. Nicotine dependence is the most common co morbidity among patients with schizophrenia, occurring in 50 to 90% of the patients[6].

Acute nicotine deprivation and withdrawal in smokers with schizophrenia has been shown to increase aggressive behavior[7], and this effect is more pronounced in individuals with higher baseline irritability or hostility[8]. Hence, forced abstinence from nicotine is associated with significant adverse outcomes and is contraindicated in this population. Nicotine replacement therapy (NRT) should be routinely offered to individuals who contemplate to quit smoking. NRT appears to be both safe and indeed imperative for successful outcomes in tobacco cessation treatment of patients with schizophrenia. The combination of nicotine transdermal patches and nicotine gum is advised. Although patients are generally discouraged from smoking while using NRT, cautiously allowing this practice appears to keep them engaged in the process, though the dangers may be overrated[9]. Care should, however, be exercised in the dosing protocol of NRT, assuring adequate nicotinic receptor saturation.

The aim of this systematic review is to systematically review the existing evidence for transdermal nicotine patches in smoking cessation among individuals with schizophrenia.

Materials and Methods

Design

A systematic review was undertaken using objective and transparent methods as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, to identify, evaluate and summarize all relevant research findings.

Structured Question

Does transdermal nicotine patches have an impact on smoking abstinence among schizophrenic population?

- PICO Analysis
  - Population: Schizophrenic population with the habit of chronic smoking
  - Intervention: NRT (Trandermal nicotine patch)
  - **C**omparison: Negative placebo (PLO)
  - Outcome: Whether there are significant changes in nicotine dependence and smoking cessation.

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Types of studies

We included double blind Randomized controlled trial studies.

The first study of the pharmacokinetics of a transdermal nicotine patch in humans was published in 1984[31] by Jed Rose, Murray Jarvik, and Daniel Rose, and was followed by publication by Rose et al. (1985) based on a study among smokers showing that transdermal nicotine patch reduced craving for cigarettes[32]. For understanding the dynamic of both transdermal nicotine patch and typical antipsychotic medications recent articles (previous 10 years) were assessed in our systematic review. Through Recent influence, we included studies from 2007-2017 concerning population of all groups. Only placebo controlled, Randomized control trials involving human population were considered. Case reports, Abstracts, Editorials, Review articles and non-English articles were excluded. Animal studies and in vitro study were not included.

Search Strategy

The literature search covered the electronic databases: PubMed and Google scholar (Image 1, Image 2). In order to search databases, strings of search (MeSH) terms, consisting of relevant text words and Boolean links, were constructed.

Database	Search pattern
PUBMED	((schizophrenic[All Fields] AND ("smokers"[MeSH Terms] OR "smokers"[All Fields])) AND (("administration, cutaneous"[MeSH Terms] OR ("administration"[All Fields] AND "cutaneous"[All Fields]) OR "cutaneous administration"[All Fields] OR "transdermal"[All Fields]) AND ("tobacco use cessation products"[MeSH Terms] OR ("nicotine dependence"[All Fields] AND "cessation"[All Fields] AND "products"[All Fields]) OR "tobacco use cessation products"[All Fields] OR ("nicotine"[All Fields] AND "patches"[All Fields]) OR "nicotine patches"[All Fields])) AND ("smoking cessation"[MeSH Terms] OR ("smoking"[All Fields] AND "cessation"[All Fields]) OR "smoking cessation"[All Fields])
EMBASE	(((schizophrenia AND (("smokers AND ("trasdermal nicotie patches" AND" smoking cessation"AND".)))
EBSCO	*ID* *Search* *S1* *MH "schizophrenic smokers"* *S2* *MH "transdermal nicotine patches" or MH "smoking cessation"* *S3* *MH "nicotine dependence".*
Google Scholar	(schizophrenic smokers OR transdermal nicotine patches OR smoking cessation OR nicotine dependence

Data Collection and Analysis

The titles and abstracts were independently identified and screened by two reviewers and search and decided on the possible reports to be included. We obtained and examined full text reports of all potentially relevant trials, to decide whether the studies fulfilled the inclusion criteria. Any disagreement between the authors was resolved through discussion.

Data Extraction

Data extraction was completed independently by the two reviewers using a specifically designed data extraction form. Quality Assessment criteria to evaluate the studies were decided by two review authors in accordance with CONSORT guidelines. The following data was collected:

- ✓ Author and Journal.
- ✓ Study design.
- ✓ Participants and groups
- ✓ Intervention
- ✓ Comparison
- ✓ Outcome
- ✓ Results

Quality Assessment

Each study was assessed using the evaluation method described in the Cochrane Handbook for Systematic Reviews (Higgins and Green. Cochrane reviewers hand

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book 2011). The quality assessment of the included trials was undertaken independently by two reviewers. The domains evaluated were randomization method, allocation concealment, assessor blinded, drop outs and risk of bias. Each domain was classified as having a low, high, or unclear risk of bias. Thus, the overall level of risk for each study was subsequently classified as low [if it did not record a "Yes" in three or more of the four main categories], "Moderate Risk" of bias [if two out of four categories did not record a "Yes"], "Low Risk" [if all the four categories recorded were adequate], "Unclear [unclear risk of bias for one or more domain].

Results

While typing the meSH terms, 20 relevant articles identified (pubmed=12, google scholar=7 trip database=1)'.Thirteen articles were eliminated after reading the title. One article eliminated due to duplication. Six articles were selected for the abstract reading. After the abstract reading one article was included and three were excluded. Four studies which met the inclusion criteria were taken for the present systematic review. (Table 1)

Types of participants

We included adult smokers with a current diagnosis of schizophrenia according to the criteria of the International Classification of Diseases (ICD) (World Health Organization 2003). We included schizophrenic population with the age group of 18-65 years. We did exclude patients with a diagnosis of schizoaffective disorder, as individuals with schizophrenia have high prevalence of additional psychiatric disorder. If a study was conducted in a group of participants with schizophrenia diagnoses, we included that trial only when separate data for people with schizophrenia were available. We included people who may or may not have expressed an interest in stopping or reducing smoking. We reported whether or not participants in a study wanted to stop or reduce smoking.

Types of interventions

We included NRT and pharmacological interventions specific to smoking cessation or reduction. Interventions intended were either placebo or other interventions (e.g. NRT antipsychotics for treating schizophrenia) which is influenced or assessed smoking abstinence or reduction outcomes were reported. The control condition could be another intervention (placebo, pharmacological).

Types of outcome measures

Primary outcome

Smoking cessation at longest follow-up

The primary outcome was smoking cessation assessed at least 3 months from the start of the intervention, according to the 'Russell Standard'[10] (i.e. a common standard for outcome criteria in smoking cessation trials). Smoking cessation could be assessed by self report or with biochemical verification.

Secondary outcomes

Smoking cessation at the end of the intervention

This was measured as for the primary abstinence outcome.

Reduction of nicotine dependence

This was assessed at the end of the intervention and during the follow-up period after the end of the intervention, if data were available. Reduction of scores on scale measures of nicotine dependence (e.g. FTND-Fragerstrom Test for Nicotine Dependence), measures that include to assess the reduction rate, carbon monoxide breath analyzer no of cigarettes per day were also assessed.

Risk of Bias

The risk of bias of the studies included in this review is summarized in Table 3 and Table 4. Out of four studies which met eligibility criteria, three studies have low risk of bias, 1 study had high risk of bias. The main risk of bias

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associated with these studies included inadequate sample size, unexplained allocation concealment.

Discussion

The systematic review was intended to assess, the efficacy of different NRT (alone or in combination with other pharmacological interventions) on smoking cessation among individuals with schizophrenia. This review has highlighted a lack of relevant research with low risk of bias on the effect of Bupropion (BUP) + Transdermal nicotine patch (TNP) ,suggesting that BUP+TNP has better smoking abstinence effect on schizophrenic population compared with placebo and TNP[11, 12].

In the present review, the search based on PRISMA guidelines narrowed down on a set of 4 randomized controlled trials that suggested a combination of TNP and sustained release of bupropion (BUP) was well tolerated, and superior to TNP and placebo for short term smoking cessation in schizophrenia.

Literature review by Freedman et al. 1995;Durany et al. 2000 have shown that nicotine increases the presynaptic & synaptic release of dopamine. Also, disordered nicotinic neurotransmission in schizophrenia patients show reduced expression of α4β2 and α7 nAChR in post-mortem brain tissue, reduced up regulation of high affinity neuronal nAChR expression in response to smoking[30], and also decrease negative symptoms of schizophrenia.

The development of medication, for the treatment of nicotine dependence in patients with schizophrenia has been a public health priority due to its high prevalence rates, devastating medical consequences, and difficulty to treat. It has been hypothesized that the high prevalence of nicotine dependence among patients with schizophrenia may be due to a shared neurobiologicalvulnerability[27]. This shared vulnerability has been evidenced in reports showing that nicotine improves neuropsychological deficits associated with schizophrenia such as in the P50 evoked auditory potentials, spatial working memory, and attention. The common pathophysiologic pathways of smoking and schizophrenia may serve as the basis for the pharmacological evaluation on medication for the treatment of these concurrent disorders. Currently, less research on medications for the treatment of this co morbidity has been conducted[29]. Studies have evaluated the efficacy of smoking cessation medications in patients with schizophrenia, these include the nicotine replacement therapy (patch, nasal spray) and sustained release bupropion. Others have evaluated the anti-smoking effect of medications (e.g., clozapine, haloperidol) used for the treatment of schizophrenia[28]. In both cases, the results have not been conclusive. Newer smoking cessation approaches such as varenicline, selegiline, rimonabant, and nicotine vaccine, among others, have yet to be tested among this population[19].

Strasser(2001), stated that existing smoking cessation guidelines do not recommend the use of bupropion in smokers with schizophrenia, because there may be a theoretical risk of psychotic relapse if bupropion, a dopamine agonist, when used among patients with schizophrenia. Some case reports have suggested that varenicline (another medication which has been proven to be effective for smoking cessation in the general population) may exacerbate psychiatric symptoms including psychosis and mood symptoms[28]. Moreover, drug treatment for smoking cessation and reduction may interact with and alter the effectiveness of the antipsychotic medications commonly prescribed patients with schizophrenia.

Interestingly, the combination of TNP+BUP doubles quit rates in comparison with TNP+placebo[9]. Since schizophrenics may smoke to alleviate withdrawal and to remediate dysfunction in nAChR and their receptor dynamics, more intensive treatment approaches such as

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TNP+BUP may have utility in the treatment of tobacco dependence in schizophrenia[11,12]. Combination therapy produces a significant enhancement of short term smoking abstinence compared to TNP alone and is well-tolerated in these patients.

Of four studies considered for evaluation only the study by George et al 2008; mentioned the age of the study population which was 18-65 years. This was a large and heterogenous population while the other three studies by A. Eden Evins et al 2007, Taryn G Moss et al 2009, Michael H Allen 2011,failed to mention the age of their study population.

The four studies included in this systematic review utilized the following methods to assess the primary outcome measures; Positive and Negative Syndrome Scale; Nicotine dependence was assessed with the Fagerström scale for Nicotine Dependence, Overt Aggression Scale(OAS scale), Behavior Scale, Richmond Agitation-Sedation Scale.

Authors Tony P George 2008, A. Eden Evins et al 2007, Michael H Allen 2011, assessed smoking cessation as a primary outcome ,while Taryn G Moss et al assessed smoking cessation as secondary outcome(5,6,7,8)with relationship between neurocognitive function and smoking cessation as the primary outcome.

Three of the studies by Taryn G Moss et al 2009, A. Eden Evins et al 2007, Michel H Allen et al 2011, used sustained release of bupropion (150 mg and 300 mg per day) as the additional pharmacological agent while one of them by Tonny p George et al 2008 used 5 or 10 mg of olanzipine orally or intramuscularly or 5mg of haloperidol intramuscularly along with sustained release of bupropion.

All the studies assessed, used transdermal nicotine patches consisting of 21 mg /24hrs and the duration of assessment were between 10-12 weeks except for the study done by Michel H Allen etal 2011 where the duration has not been specified[9,10,11,12].

The rate of relapse of smoking was reported in both the test and control groups across all the 4 studies. This was found to be high during tapering and discontinuation of pharmacological treatment. Those on bupropion SR, nicotine patch 21 mg/d, and nicotine gum up to 18 mg/d had a 4-week continuous abstinence rate of more than 50 %[10].

Although relapse rates are considerably high in the general population after short-term discontinuation in smoking cessation treatment, the nicotinic receptor expression does not return to normal after smoking cessation in smokers without schizophrenia. In schizophrenia, nicotinic activity is abnormally low at baseline, which is increased by smoking or NRT, and is not expected to return to a normal baseline after smoking cessation.

One of the four studies evaluated the medication compliance, smoking abstinence, psychiatric symptoms and medication related adverse effects, quantitatively. All four studies stated the combination of TNP and sustained release of bupropion (BUP) was well tolerated, and superior to TNP and placebo for short term smoking cessation in schizophrenia.

One of the studies by A. Edvin Evins et al 2007, measured Smoking abstinence by using CO breath analyzer-6(38%), 8 (23%), 38 patients were abstained. TarynG Moss et al 2009, assessed the smoking abstinence by an absence of self-reported cigarette use in the seven day prior to,and including the day of assessment. These verbal reports were biologically confirmed weekly by CO<10 ppm(George et al 2002 a). T P George 2008, assessed the relapse rate by pill counts and urinary riboflavin.

Quality assessment of the studies showed that among four trials, three studies showed low risk of bias. However, there was a difference in the intervention measurement

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methods, outcome assessments, and follow up period, randomization and blinded methods which could affect the trial results.

Relative risk assessment was done among three out of four trials. The evidence has been showed that quit rate in NTP+PLO was less compared to NTP+BUP. Risk ratio were calculated by using Revman software (V 5.2), and the following were the relative risk ratios (8.00, 9.67, 4.16)[18,16,11] of the included studies respectively. The fourth trial done by Michael H Alen et al, whose results showed that, there was a significant difference in reduction between nicotine and placebo groups at 4 hours(t=2.74,p=0.010) and at 24 hours (t=3.08, p=0.004).This study did not provide adequate information for relative risk assessment in this systematic review.

Limitations of these studies include: 1) sample size, 2) lack of applicability to the typical outpatient smoker without schizophrenia.

Synthesis of Results: There was no heterogeneity between trials (Heterogeneity chisquared = 0.99), and a fixed-effects model showed that the BUP+TNP interventions did not influence the smoking abstinence [= 1.00; 95% confidence interval (CI) (0.40, 2.49)] (figure 1)

Risk of Bias across Controlled Clinical Trials: Meta-regression or statistical assessment of publication bias was not performed due to the limited number of trials and minimal variability in terms of duration or quality of the randomized trials.

Quality assessment was done by using Cochrane Handbook (2011) for Systematic Reviews (Higgins and Green) based on which three of four studies included in our review showed a low risk of bias. These articles assessed the efficacy of NTP, on assessment the quit rate in NTP+PLO was less compared to NTP+BUP which is substantiated by the relative risk for each of the articles. NTP helps in smoking cessation /and reducing nicotine dependence, but when used in conjugation with the pharmacotherapy's such as bupropion & varenicline it has shown a better rate of smoking cessation /and reducing nicotine dependence among schizophrenic population.

Since the population under consideration was schizophrenic most articles support a multi-pronged approach (NTP+pharmacotherapy) for better outcome in quit rate of smoking among them.

Conclusion

Table 2: guideline table

Author name ,Year	Study population	Intervention	Objectives	Outcome and result	anticipated absolute effect	Relative effect	Number of participants	Comments
Tony P. George, M.D., FRCPC(2008)	smokers with schizophrenia sample - 58	21mg/ day 12 (around 3months) weeks. sustained-release (SR) bupropion	To examined the relationship between neurocognitive function and smoking cessation in	For continuous abstinence (Days 43-70), 8/29 (27.6%) subjects on BUP+TNP and 1/29 (3.4%) on PLO+TNP were abstinent (OR 10.67,	Quit rate of smoking in case(27.5%) (-) quit rate of smoking in control(3.44%) =24.2%	COHORT QUIT (cases /control*) 8.00	Cases (BUP+TNP)-29 8-quitted smoking. Control (PLO+TNP)-29 1 –quitted smoking.	Combination therapy with bupropion SR+TNP versus placebo+T

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		(300 mg/ day) Case – BUP+TNP Control- TNP+PLO	schizophrenia.	95% CI 1.24, 91.98; Fisher's Exact Test, p<0.03; NNT 5, 95% CI 2.4, 15.2). For trial endpoint (Week 10) abstinence, 10/29 (34.5%) on BUP +TNP, and 3/29 (10.3%) on PLO+TNP met trial endpoint abstinence (OR 4.56, 95% CI 0.96, 18.86; Fisher's Exact Test, p=0.056; NNT 5, 95% CI 2.2, 27.8).				NP is well tolerated and leads to significant improvement in short-term smoking abstinence outcomes in smokers with schizophrenia. The combination was well-tolerated in schizophrenic smokers
Taryn G. Moss(2009)	Smokers with schizophrenia sample - 58	21mg/ day 12 (around 3months) weeks. Sustained-release (SR) bupropion. Case – BUP+TNP Control- TNP+PLO	To examined the relationship between neurocognitive function and smoking cessation in schizophrenia.	Subjects were compared as a function of endpoint smoking status . no significant baseline differences between quitters and non-quitters, non-quitters exhibited significantly greater deficits in performance on TMT-B (p=0.01) and on Digit Span backwards (p=0.04) compared to quitters.	Quitted smoking in case (32.2%) (-) quitted smoking in control (0%) = 32.2%	COHORT QUIT (cases /control*) 9.67	Cases (BUP+TNP)-31 10-quitted smoking. Control(PLO+TNP)-27 no –quitted smoking.	Findings extend results of previous studies which suggest deficits in frontal executive function are associated with smoking cessation failure in schizophrenia. This may have implications for the development of tailored smoking cessation treatments in schizophrenic population.

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Michael H. Allen, M.D. et al(2011)	Schizophrenic patients with the habit of smoking Age -18-65 years Sample -40	10 week (around 3 months)of treatment with the transdermal nicotine patch (21mg/ day) Bupropion SR 150 mg,5 or 10 mg of olanzapine orally or intramuscularly or 5 mg of haloperidol intramuscularly Case – BUP+TNP OR 5 or 10 mg of olanzapine OR 5 mg of haloperidol Control- TNP+PLO	To find the reduction of agitation and aggression in smokers with schizophrenia and nicotine dependence.	Nicotine replacement group was 33% lower nicotine dependence at 4 hours and 23% lower nicotine dependence at 24 hours than for the placebo group.	NOT estimated.	There was a significant difference in reduction between nicotine and placebo groups at 4 hours(t=2.74,p= 0.010) and at 24 hours (t=3.08, p=0.004).	Cases-20, Controls-20.	Patients with schizophrenia, smoking status should be included in the assessment of agitation and nicotine replacement included in the treatment of those who are smokers Participants with lower levels of nicotine dependence responded better than those with higher levels of dependence
A. Eden Evins, MD, MPH (2007)	Schizophrenic patients with the habit of smoking Sample-51	placebo added to transdermal nicotine patch 21mg/ 24 hrs, nicotine polacrilex gum, and CBT bupropion SR 300 mg/day. Case – BUP+TNP Control- TNP+PLO	To examine whether there is a benefit of adding bupropion SR to high-dose combination nicotine replacement therapy (NRT) and weekly group cognitive behavioral therapy (CBT) for smoking reduction or cessation in schizophrenia.	From baseline to Week 12, subjects on bupropion + NRT had a mean change of 21 (95% CI, 29–15) cigarettes per day, and those on placebo had a mean change of 11 (95% CI, 26 to 4.8) cigarettes per day. At the end of 24 th week in the bupropion NRT group had a change from baseline of 9.5 (95% CI, _19 to 0.4) cigarettes per day, and those in the placebo + NRT	Quit rate of smoking in case (32%) (-)quit rate of 0smoking in control(7.6%) = 24.33%	COHORT QUIT (cases /control*)-4.16	Cases (BUP+TNP)-25 8-quitted smoking. Control (PLO+TNP)-26 2 –quitted smoking.	Schizophrenia patients have decreased nicotinic receptor expression and function, longer duration treatment with tailored nicotine dependence. treatment with high-

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				group reported a mean change of 2.9 (95% CI, 24 to 18) cigarettes per day.				dose NRT, combination of short- and long-acting NRT, and/or combination bupropion and NRT may improve sustained abstinence rates.

Table 3- Risk of Bias of the Included Study

Major Criteria

S. No	Study	Randomization	Allocation Concealment	Assessor Blinded	Drop outs Described	Risk of Bias
1	A Placebo-Controlled Trial of Bupropion Combined with Nicotine Patch for Smoking Cessation in Schizophrenia Tony P. George, M.D., FRCPC	YES	NO	YES	YES	LOW
2	Prefrontal Cognitive Dysfunction is Associated with Tobacco Dependence Treatment Failure in Smokers with Schizophrenia Taryn G. Moss	NO	NO	YES	NONE	LOW
3	Effect of Nicotine Replacement Therapy on Agitation in Smokers With Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Study, Michael H. Allen, M.D.	YES	NO	YES	YES	LOW
4	A 12-Week Double-Blind, Placebo-Controlled Study of Bupropion SR Added to High-Dose Dual Nicotine Replacement Therapy for Smoking Cessation or Reduction in Schizophrenia. A. Eden Evins, MD, MPH	YES	NO	YES	YES	MODERATE

Minor Criteria

S .No	Study	Sample justified	Baseline comparison	I/E criteria	Methods of error
1	A Placebo-Controlled Trial of Bupropion Combined with Nicotine Patch for Smoking Cessation in Schizophrenia Tony P. George, M.D., FRCPC	NO	YES	YES	NO
2	Prefrontal Cognitive Dysfunction is Associated with Tobacco Dependence Treatment Failure in Smokers with Schizophrenia Taryn G. Moss	NO	YES	YES	NO
3	Effect of Nicotine Replacement Therapy on Agitation in Smokers With Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Study, Michael H. Allen, M.D.	NO	YES	YES	NO
4	A 12-Week Double-Blind, Placebo-Controlled Study of Bupropion SR Added to High-Dose Dual Nicotine Replacement Therapy for Smoking Cessation or Reduction in Schizophrenia. A. Eden Evins, MD, MPH	YES	YES	YES	NO

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Table-4: Quality of Evidence of the Assessed Studies

High risk of bias (Low evidence)	Moderate risk of bias (Moderate evidence)	Low risk of bias (High evidence)
If it did not record a "YES" in three or more of the four main categories	If two out of four categories did not record a "YES"	If all the categories recorded a "YES"
1 STUDY	NO STUDIES	3 STUDIES
1. Prefrontal Cognitive Dysfunction is Associated with Tobacco Dependence Treatment Failure in Smokers with Schizophrenia Taryn G. Moss		1. A Placebo-Controlled Trial of Bupropion Combined with Nicotine Patch for Smoking Cessation in Schizophrenia Tony P. George, M.D., FRCPC 2. Effect of Nicotine Replacement Therapy on Agitation in Smokers With Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Study, Michael H. Allen, M.D. 3. A 12-Week Double-Blind, Placebo-Controlled Study of Bupropion SR Added to High-Dose Dual Nicotine Replacement Therapy for Smoking Cessation or Reduction in Schizophrenia. A. Eden Evins, MD, MPH

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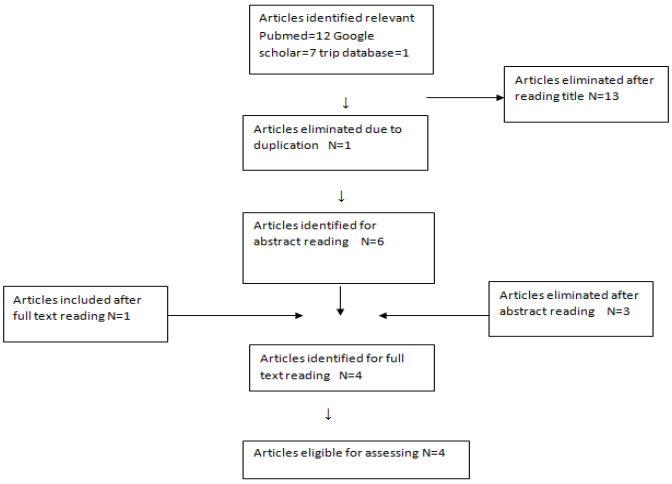
Table 1: Flow chart (selection of studies)



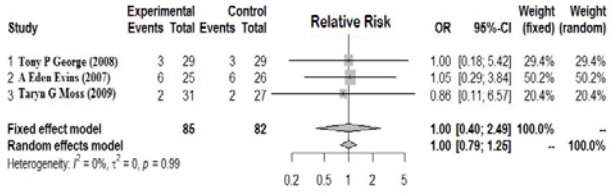


Figure 1: Forest plot displaying the impact of TNP+BUP effect on smoking abstinence scores for included randomized controlled trials. Sample sizes displayed are effective sample sizes which differs from actual sample sizes in trials. fixed-effects models lead to the consistent conclusion that smoking abstinence was not influence the intervention. Included studies did not show statistically significant heterogeneity hence, fixed-effect model was used.

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