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Effectiveness of multimodal interventions focused on smoking cessation in patients with schizophrenia: A systematic review

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ABSTRACT

Background: Smoking is a significant risk factor for mortality and morbidity among patients with schizophrenia.
Objective: To clarify the effectiveness of multimodal smoking cessation interventions in adult smokers diagnosed with schizophrenia.
Methods: A systematic review was conducted according to PRISMA guidelines. Relevant electronic databases were searched for clinical trials that combined pharmacological and non-pharmacological smoking cessation interventions for patients with schizophrenia, published up to October 2020. Primary outcomes were smoking abstinence and smoking reduction. Secondary outcomes consisted in psychiatric symptoms.
Results: A final sample of nine articles was obtained from a total of 208 studies. All studies reported higher biochemically validated smoking reduction rates after treatment. However, the majority of the studies reported low smoking abstinence rates, which progressively decreased over time. Multimodal interventions did not worsen psychiatric symptoms.
Conclusion: Evidence suggests that multimodal smoking cessation interventions for individuals diagnosed with schizophrenia should be recommended by clinicians, as they showed to be effective in reducing smoking without worsening psychiatric symptoms. Further studies are needed to understand how interventions can become more effective in helping patients achieve long-term smoking abstinence.

1. Introduction

Schizophrenia is a chronic mental illness characterized by recurrent psychosis that can be manifested by delusions, hallucinations, disorganized thought and speech processes, and/or negative symptoms such as lack of motivation, emotional and social withdrawal (American Psychiatric Association, 2013). It is one of the most debilitating diseases displaying a wide range of disability in both cognitive domains and everyday functioning, with a worldwide lifetime prevalence of 1% (Strous and Shoenfeld, 2006). It is also associated with an increased prevalence of smoking, which is considered a modifiable lifestyle and a risk factor by the World Health Organization (Prince et al., 2007; WHO, 2009). Patients with schizophrenia smoke more and extract more nicotine from each cigarette, experiencing a more severe nicotine dependence than the general population, and even than patients diagnosed with other mental illnesses (Correll, 2007; de Leon and Diaz, 2005; Tsoi et al., 2010). Smoking prevalence among adults in the United States was 15.5% in 2016, which contrasts with a prevalence of over 60% among patients diagnosed with schizophrenia (Dickerson et al., 2018; Jamal et al., 2018).

There are some well-founded reasons based on the pathophysiology of schizophrenia that underlie the premise that tobacco compensates downregulated dopamine expression and receptors in the brain (Keltner and Grant, 2006). Some studies showed that nicotine augments the release of dopamine in the nucleus accumbens and in the prefrontal cortex (Corrigall, 1991; Imperato et al., 1986). Dopaminergic stimulation improves motivation, mood and cognition (which can be affected in these patients), and also decreases appetite (treatment under atypical antipsychotics can lead to weight gain) (Glassman, 1993; Kavanagh et al., 2002; Keltner and Grant, 2006; Lohr and Flynn, 1992). Another biological effect is related to nicotine ability to improve acetylcholine functioning, leading to an attenuation of the patients' struggle to screen out unwelcome background noise that is usually associated with debilitated attention and auditory hallucinations (Glassman, 1993; Kavanagh et al., 2002; Lohr and Flynn, 1992).

All of these factors help to understand the low worldwide smoking cessation prevalence among patients with schizophrenia (14%) reported in a recent meta-analysis (Zeng et al., 2020). This prevalence was significantly lower compared to healthy controls and to patients

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with other psychiatric disorders (Zeng et al., 2020). The literature points out other reasons, not related to the mechanisms of the disease, that help to understand why patients with schizophrenia have more difficulties in quitting smoking, such as lack of adequate advice and structured medical assistance regarding smoking abstinence, lack of information about abstinence treatments, and clinicians' fear of intensifying patients' aggressive behaviors or psychotic symptoms (Addington, 1998; Lan et al., 2007; Landow et al., 1995; Mitchell et al., 2015; Williams and Ziedonis, 2006).

Schizophrenia is related to a 20% decrease on life expectancy (Williams and Foulds, 2007). Chronic smoking enhances this burden, as it increases significantly the mortality rate (particularly cardiac, respiratory and cancer mortality) among these individuals, compared to the mortality rate of patients diagnosed with schizophrenia who do not smoke (Beary et al., 2012; Els, 2004; Kelly et al., 2011; Piotrowski et al., 2017). Tobacco also aggravates the morbidity associated with schizophrenia. For instance, it can provoke an impairment of cognitive function such as working memory, and a requirement of higher daily doses of neuroleptics due to pharmacokinetic interactions, therefore increasing the rate of tardive dyskinesia (Barnes et al., 2006; de Leon and Diaz, 2005; Lee et al., 2015; Yassa et al., 1987). In view of these consequences, offering smoking cessation advice has to be seen by clinicians as a priority in the management of patients with schizophrenia (Mitchell et al., 2015; Stubbs et al., 2015). Thus, the hypothesis that quitting smoking may improve mental health symptoms is starting to be raised (Minichino et al., 2013).

A growing body of evidence shows the efficacy of varenicline, sustained-release bupropion, and nicotine replacement therapy (NRT) as first-line, well-tolerated and safe smoking cessation pharmacotherapies for individuals with schizophrenia (Ahmed et al., 2018; Els, 2004; Freedman et al., 1995; Smith et al., 2016; Tsoi et al., 2010). A recent meta-analysis found that none of the agents provoked changes in psychiatric symptoms, but varenicline was associated with higher rates of nausea than was placebo (Siskind et al., 2020). Clinicians should encourage smoking cessation without the fear of nicotine withdrawal symptoms and adverse effects (Barnes et al., 2006). However, health professionals should also keep in mind that a forced abstinence from nicotine can be responsible for adverse outcomes and is contraindicated for patients with schizophrenia (Els, 2004). Promoting physical activity to help antagonize the potential weight gain and diabetes risk following smoking cessation can also be an ally on quitting smoking (Stubbs et al., 2015). Also, contingency management has long been recognized as an effective supplement to pharmacotherapy for substance use disorders, enhancing treatment adherence (Carroll and Rounsaville, 2007; Higgins et al., 1994). Evidence suggests that the previously described pharmacologic treatments combined with behavioral therapy for smoking cessation is effective among smokers with schizophrenia spectrum disorders, although more long-term research is required (Caponnetto and Polosa, 2020). Therefore, a systematic review was conducted to examine the best available clinical evidence on smoking cessation interventions that integrate pharmacologic and non-pharmacologic treatments in patients with schizophrenia. This systematic review aims to clarify the effectiveness of multimodal smoking cessation interventions in adult smokers diagnosed with schizophrenia.

2. Material and methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.1. Inclusion criteria

Inclusion criteria were as follows: (1) Study design: clinical trials; (2) Participants: adults (≥ 18 years old) diagnosed with schizophrenia spectrum disorders, who were current smokers, and had the capacity to consent at the time of recruitment; (3) Intervention: multimodal interventions (combining pharmacological and non-pharmacological treatments); (4) Comparison group: placebo control, other active intervention for smoking cessation, or no comparison group; (5) Outcomes: the primary outcomes were smoking abstinence (self-reported smoking status and/or biochemically validated measures) and smoking reduction (reduction in the number of cigarettes smoked per day and/or biochemically validated measures); the secondary outcomes were psychiatric symptoms associated with schizophrenia, such as positive and negative symptoms, depressive symptoms, anxiety symptoms, extrapyramidal symptoms, akathisia, and neuropsychological performance.

2.2. Exclusion criteria

Exclusion criteria were as follows: Studies with no experimental intervention in humans; Case reports; Clinical trials that span a population diagnosed with psychotic disorders other than schizophrenia spectrum disorders, or with criteria for substance abuse or dependence other than nicotine.

2.3. Search strategy

Evidence was electronically searched in PubMed, Scopus, ISI Web of Science, and PsycInfo from database inception to October 9th, 2020, using the following search strings (including MeSH terms and non-Mesh terms adapted for each database): ((“Psychotic Disorders”[Mesh]) OR (“Schizophrenia”[Mesh]) OR “Schizoaffective disorder” OR “Schizophrenia spectrum”)) AND ((“Smoking Cessation/methods”[Mesh]) OR (“Tobacco Smoking/therapy”[Mesh]) OR (“Smoking Cessation Agents”[Mesh]) OR “Smoking Cessation therap*” OR “Tobacco Cessation therap*”)).

No articles were excluded on the basis of date, language, or duration of the trial. Electronic searches were supplemented by hand searching reference lists of retrieved papers.

2.4. Study selection

Records were selected by screening title, abstract, and inclusion/exclusion criteria. Full-text of the studies that potentially met the eligibility criteria was obtained. Two authors independently extracted all studies in duplicate, resolving disagreements by discussion with a third author if necessary. Articles were checked for duplication of the same data.

2.5. Data extraction

The data extraction was based on the inclusion/exclusion criteria, and on the search protocol development. The EndNote® tool was used to analyze and select the studies, and an Excel® sheet was used to record the article selection steps. The following data was extracted from each trial: author; year of publication; study characteristics; sample size; diagnosis; participants' characteristics; intervention characteristics; control condition; primary and secondary outcomes; and main results. No meta-analysis was used due to the heterogeneity of both intervention and comparison groups.

3. Results

3.1. Study selection

A total of 206 records were gathered from the electronic search of the following databases (130 from PubMed, 21 from Scopus, 49 from Web of Science, and 6 from PsycInfo). Two more trial reports were identified from hand searching. Of the 208 records included, 29 were duplicates. Thus, 179 records were screened and then excluded based on the relevance of title and abstract. A final selection of 25 full-text articles

was assessed for eligibility for inclusion, which resulted in 9 clinical trials that fulfilled the inclusion criteria. Fig. 1 demonstrates a PRISMA flow diagram that describes the search process that enabled the selection of the articles included in this systematic review.

3.2. Studies characteristics

Table 1 describes the features of the clinical trials based on PICOS (population, interventions, comparisons, outcomes and study design) criteria. All 9 trials analyzed the combined effect of multimodal interventions (pharmacological and non-pharmacological) among patients diagnosed with schizophrenia spectrum disorders (schizophrenia and schizoaffective disorder). It will be used the term schizophrenia to refer to patients who have the diagnosis of schizophrenia or schizoaffective disorder, because no apparent differences are known regarding smoking behaviors and treatments for individuals with these psychotic subtypes (McChargue et al., 2002). The studies varied in their size, design, and type of intervention. Included studies were conducted across two countries (USA and Canada) and published between 1998 and 2012. Study designs included mostly randomized controlled trials (Evins et al., 2007; George et al., 2000; Tidey et al., 2011; Weiner et al., 2001; Williams et al., 2010), and sample sizes ranged from 8 to 87. All studies recruited participants from outpatient mental health facilities, although two studies did not report recruitment setting (Addington et al., 1998; Weiner et al., 2012). Seven studies examined individuals with schizophrenia spectrum disorders, and two studies only included participants with schizophrenia diagnosis (Evins et al., 2007; Evins et al., 2001). Studies were based on the following non-pharmacological intervention protocols: Cognitive behavioral therapy (CBT) (Evins et al., 2007; Evins et al., 2001); Behavioral therapies, such as the American Lung Association (ALA) program that emphasizes positive reinforcement, psychoeducation, and anxiety reduction strategies (Addington et al., 1998; George et al., 2000), a Specialized schizophrenia smoking cessation program, which includes motivational enhancement therapy, relapse prevention strategies, psychoeducation, and social skills training (George et al., 2000), Treatment of addiction to nicotine in schizophrenia (TANS), which incorporates motivational interviewing skills, social skills training, and relapse prevention techniques (Williams et al., 2010), Medication management (MM), which emphasizes medication compliance and education about NRT (Williams et al., 2010); Contingency management therapy (CM) based on providing a tangible reinforce upon the objective confirmation of smoking abstinence (Tidey et al., 2002; Tidey et al., 2011); Non-contingent reinforcement intervention (NR) (Tidey et al., 2002; Tidey et al., 2011); and Supportive therapy (Weiner et al., 2012; Weiner et al., 2001). Six interventions were delivered in groups (Addington et al., 1998; Evins et al., 2007; Evins et al., 2001; George et al., 2000; Weiner et al., 2012; Weiner et al., 2001), while three studies delivered individual interventions (Tidey et al., 2002; Tidey et al., 2011; Williams et al., 2010).

Four studies were of bupropion (Evins et al., 2001; Tidey et al., 2011; Weiner et al., 2012; Weiner et al., 2001), four studies were of NRT (Addington et al., 1998; George et al., 2000; Tidey et al., 2002; Williams et al., 2010), and one study combined bupropion with NRT (Evins et al., 2007). Of these, three studies compared bupropion versus

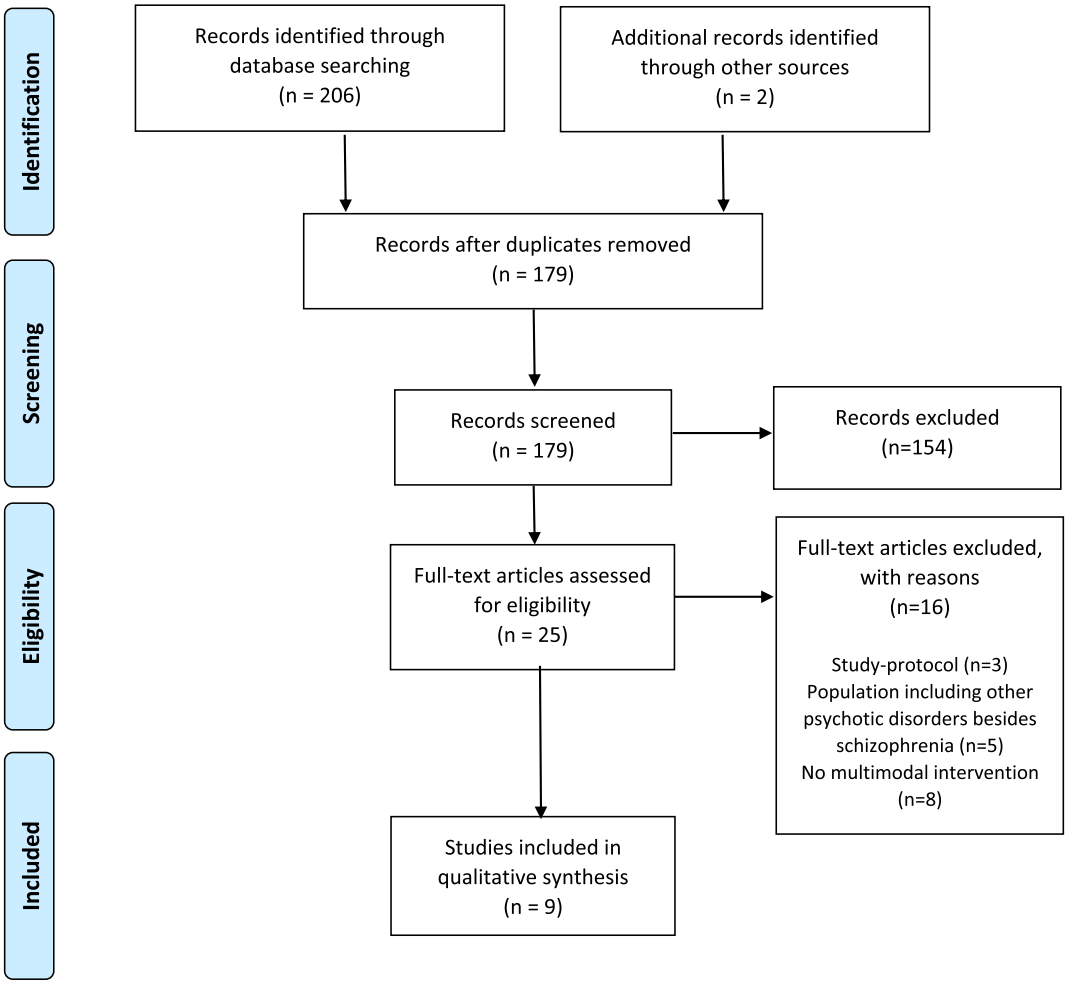

Fig. 1. PRISMA flow diagram of the literature search process.

Table 1
Characteristics of smoking cessation clinical trials for patients with schizophrenia spectrum disorders.

Study (location)	Study design	Participants (n)	Non-pharmacological intervention (n)	Pharmacological intervention	Control condition (n)	Pharmacological intervention in the control condition	Follow-up	Primary outcomes	Secondary outcomes	Results
Addington et al., 1998 (Canada)	Uncontrolled clinical trial	Schizophrenia or schizoaffective disorder; Nicotine dependence ($n = 50$) DSM-IV	Group therapy adapted from ALA program ($n = 50$) 7 sessions (weekly, 75 min)	NRT (Nicotine patch): 21 mg/d for 6 wk., 14 mg/d for 2 wk., and 7 mg/d for 2 wk	None	None	3 and 6 months	7-d point prevalence abstinence (self-reported and urinary cotinine)	Positive and negative symptoms (PANSS), extrapyramidal symptoms (SAS)	A significant number of patients quitted smoking after the intervention (42%), with a progressive decrease at follow-ups (16% at 3-month and 12% at 6-month). No significant differences in psychiatric symptoms prior and after the intervention.
Evins et al., 2001 (USA)	Pilot trial	Schizophrenia; Nicotine dependence ($n = 18$) DSM-IV > 10 cig/d	CBT Group program (n = 9) 9 sessions (weekly, 60 min)	Bupropion: 150 mg/d for 12 wk.	CBT Group program ($n = 9$) 9 sessions (weekly, 60 min)	Placebo for 12 wk	3 months	Point prevalence abstinence (expired-air CO or serum cotinine); Significant smoking reduction (50% reduction in self-report of cigarettes smoked per day +30% reduction in expired-air CO)	Positive symptoms (BPRS), negative symptoms (SANS), depressive symptoms (HamD), extrapyramidal symptoms (SAS), and akathisia (HAS)	The bupropion group showed a significantly higher smoking reduction than the placebo group (66% vs 11%), and that effect persisted at follow-up (33.3% vs 11%). One subject (11%) in the bupropion group (and no subjects in the placebo group) achieved abstinence. Negative symptoms improved in the bupropion group. Positive and depressive symptoms increased significantly in the placebo group. No differences found between groups in extrapyramidal symptoms and akathisia.
Evins et al., 2007 (USA)	RCT	Schizophrenia; Nicotine dependence ($n = 51$) DSM-IV ≥ 10 cig/d	CBT Group program 12 sessions ($n = 25$) (weekly, 60 min)	Bupropion: 150 mg/d for 7 days, 300 mg/d for 11 wk. + NRT: nicotine patch 21 mg/d for 4 wk., 14 mg/d for 2 wk., 7 mg/d for 2 wk. + Nicotine gum (2 mg) distributed as needed to 18 mg/d	CBT Group program 12 sessions ($n = 26$) (weekly, 60 min)	Placebo: once a day for 7 days, twice a day for 11 wk. + NRT: nicotine patch 21 mg/d for 4 wk., 14 mg/d for 2 wk., 7 mg/d for 2 wk. + Nicotine gum (2 mg) distributed as needed to 18 mg/d	3 and 12 months	7-d point prevalence smoking reduction (50% to 100% reduction in cigarettes smoked per day + ≥ 40% reduction of expired air CO); 7-d point prevalence abstinence (expired air CO < 8 ppm)	Positive symptoms (PANSS), negative symptoms (SANS), depressive symptoms (HamD), anxiety symptoms (STAI), extrapyramidal symptoms (SAS), and akathisia (BAS)	Bupropion + NRT showed a superior effect on smoking reduction than placebo + NRT at the end of the treatment (60% vs 31%), and at 3-month follow-up (32% vs 8%). Abstinence rates did not differ between groups after treatment and at follow-ups. Akathisia and extrapyramidal symptoms decreased in the bupropion group and increased in the placebo group.
George et al., 2000 (USA)	RCT	Schizophrenia or schizoaffective disorder; Nicotine dependence ($n = 45$) DSM-IV FTND ≥5	Group therapy adapted from the ALA program + supportive group counselling ($n = 17$) 10 sessions (weekly, 60 min)	NRT (24-h nicotine transdermal patch): 21 mg/d for 6 wk., 14 mg/d for 2 wk., and 7 mg/d for 2 wk	Group therapy based on a specialized schizophrenia smoking cessation program ($n = 28$) 10 sessions (weekly, 60 min)	NRT (24-h nicotine transdermal patch): 21 mg/d for 6 wk., 14 mg/d for 2 wk., and 7 mg/d for 2 wk	6 months	Point prevalence abstinence (expired air CO and self-reported cigarette use)	Positive and negative symptoms (PANSS), extrapyramidal symptoms (WEPS)	Smoking abstinence rates and psychiatric symptoms did not differ between both groups (35.3% in the ALA group vs 35.7% in the specialized group). Abstinence rates decreased from the end of the treatment to the 6-month follow-up.

Tidey et al., 2002 (USA)	Non-RCT	Schizophrenia or schizoaffective disorder; Nicotine dependence (n = 14) FTND ≥6 CO levels ≥18 ppm	Condition 1: CM intervention (n = 14) 5 days	Condition 1: NRT (nicotine patch): 21 mg/24 h for 5 days	Condition 2: CM intervention (n = 14) 5 days; Condition 3: NR intervention (n = 14) 5 days	Condition 2: Placebo patch for 5 days; Condition 3: Placebo patch for 5 days	2 weeks	Smoking reduction (breath CO ≤ 11 ppm; salivary cotinine levels)	None	Smoking decreased considerably in CM conditions (33% to 40% of occasions over a 5-day period with CO levels below the cutoff), but NRT did not increase the efficacy of CM intervention.
Tidey et al., 2011 (USA)	RCT	Schizophrenia or schizoaffective disorder; Nicotine dependence (n = 52) DSM-IV FTND ≥6 ≥ 20 cig/d	Group 1: CM intervention (n = 12) 22 days	Group 1: Bupropion: 150 mg/d for 3 days, 300 mg/d for 18 days	Group 2: CM intervention (n = 16) 22 days; Group 3: NR intervention (n = 11) 22 days; Group 4: NR intervention (n = 13) 22 days	Group 2: Placebo once a day for 3 days, twice a day for 18 days Group 3: Bupropion: 150 mg/d for 3 days, 300 mg/d for 18 days Group 4: Placebo once a day for 3 days, twice a day for 18 days	None	Smoking reduction (Urinary cotinine; Breath CO; number of cigarettes smoked per day)	Positive, negative symptoms (PANSS), Movement disorders (UPDRS, AIMS)	Cotinine and CO levels were significantly lower in participants randomized to the CM conditions (reduction of 30%), but not to the NR condition. Bupropion did not reduce smoking or increase the efficacy of CM intervention. Psychiatric symptoms significantly decreased in all conditions.
Weiner et al., 2001 (USA)	Open-label clinical trial	Schizophrenia or schizoaffective disorder; Nicotine dependence (n = 8) DSM-IV	Supportive group therapy adapted from the American Cancer Society Fresh Start Program (n = 8) 9 sessions (weekly)	Bupropion: 150 mg/d for 3 days, 150 mg/twice a day for 11 wk	None	None	None	End expired breath CO	Positive, depressive, and anxiety symptoms (BPRS), negative symptoms (SANS), neuropsychological functioning	A significant decrease in CO levels was reported (mean of change 21.06 ppm), without any worsening in psychiatric and cognitive symptoms. None of the participants achieved smoking abstinence.
Weiner et al., 2012 (USA)	RCT	Schizophrenia or schizoaffective disorder; Nicotine dependence (n = 31) DSM-IV ≥ 10 cig/d	Support group 9 weeks	Bupropion 12 weeks	Support group 9 weeks	Placebo 12 weeks	None	4 weeks sustained abstinence	Psychiatric symptoms, and neuropsychological performance	No significant differences found in smoking outcomes between groups. No significant changes reported in psychiatric symptoms and neuropsychological performance.
Williams et al., 2010 (USA)	RCT	Schizophrenia or schizoaffective disorder; Nicotine dependence (n = 87) DSM-IV > 10 cig/d	Individual TANS (n = 45) 24 sessions (over 26 wk.; 45 min)	NRT (Nicotine transdermal patch): 21 mg for 12 wk., and 14 mg for 4 wk	Individual MM (n = 42) 9 sessions (over 26 wk.; 20 min)	NRT (nicotine transdermal patch): 21 mg for 12 wk., and 14 mg for 4 wk	3, 6 and 12 months	Continuous abstinence (self-reported point prevalence abstinence after quit date, Exhaled CO); Smoking reduction (number of cigarettes smoked per day, expired CO)	Positive, negative (PANSS), and depressive (BDI) symptoms	A significant number of patients quitted smoking in both groups, with a progressive decline in abstinence rates over time (21% at 3-month and 17% at 6-month), with abstinence at 12-month follow-up not significantly different between groups. Subjects in both groups significantly reduced smoking. No differences found in psychiatric symptoms between groups.

Note: RCT = Randomized Controlled Trial; CO=Carbon monoxide; ALA = American Lung Association; CBT = Cognitive Behavioral Therapy; NRT = Nicotine Replacement Therapy; PANSS=Positive and Negative Syndrome Scale; BPRS=Brief Psychiatric Rating Scale; SAS=Simpson-Angus Scale; SAS=Scale for the Assessment of negative symptoms; HamD=Hamilton Depression Rating Scale; HAS=Hillside Akathisia Scale; FTND=Fagerström Test for Nicotine Dependence; CM = Contingency Management; NR = Non-Contingent Reinforcement; STAI=State-Trait Anxiety Inventory; BAS=Barnes Akathisia Scale; WEPS=Webster Extrapyramidal Symptoms Scale; UPDRS=Unified Parkinson's Disease Rating Scale; AIMS = Abnormal Involuntary Movement Scale; TANS = Treatment of Addiction to Nicotine in Schizophrenia; MM = Medication Management; BDI=Beck Depression Inventory.

placebo (Evins et al., 2001; Tidey et al., 2011; Weiner et al., 2012), one study compared NRT versus placebo (Tidey et al., 2002), and one study compared bupropion + NRT versus placebo + NRT (Evins et al., 2007).

3.3. Outcomes

The main outcomes measures were smoking abstinence and smoking reduction at the end of the treatment and at follow-ups. Most studies included a 3-month follow-up, whereas three studies did not include follow-up measures (Tidey et al., 2011; Weiner et al., 2012; Weiner et al., 2001). Eight studies confirmed smoking outcomes using biochemical markers (cotinine, expired-air carbon monoxide - CO), although one study did not report abstinence measures (Weiner et al., 2012). Only one study did not include psychiatric symptoms as secondary outcomes (Tidey et al., 2002). The Positive and Negative Syndrome Scale (PANSS) was the most used instrument to assess positive and negative symptoms (Addington et al., 1998; Evins et al., 2007; George et al., 2000; Tidey et al., 2011; Williams et al., 2010). Depressive symptoms were assessed in four studies (Evins et al., 2007; Evins et al., 2001; Weiner et al., 2001; Williams et al., 2010), mostly by the Hamilton Rating Scale for Depression (HamD). Anxiety symptoms were assessed by the State-Trait Anxiety Inventory (STAI) (Evins et al., 2007), and by the Brief Psychiatric Rating Scale (Weiner et al., 2001). Extrapyramidal symptoms were assessed in four studies (Addington et al., 1998; Evins et al., 2007; Evins et al., 2001; George et al., 2000), mostly by the Simpson-Angus Rating Scale (SAS). Akathisia was assessed in two studies by the Hillside Akathisia Scale (Evins et al., 2001), and by the Barnes Akathisia Scale (Evins et al., 2007). One study (Tidey et al., 2011) assessed movement disorders, and two studies assessed neuropsychological functioning by a brief neuropsychological test battery (Weiner et al., 2012; Weiner et al., 2001).

3.4. Quality of the articles

The evaluation of the quality of the studies was assessed using the Jadad Scale (Table 2) (Jadad et al., 1996). We intended to include all the papers on the topic regardless of the Jadad score due to the limited number of trials. The 9 clinical trials scored between 1 and 4 points. The ones with a considerable risk for bias did not have a control group or had participants who were not randomized to the intervention. In literature, blinding of participants and providers on psychological treatments is a challenge. Four studies were double-blind clinical trials, with only one study describing the method of double-blinding. Eight papers mentioned withdrawals and dropouts, with the underlying reasons.

3.5. Effectiveness of interventions

Multimodal smoking cessation interventions were grouped following the pharmacological interventions used (bupropion combined with non-pharmacological interventions and NRT combined with non-pharmacological interventions).

3.5.1. Bupropion combined with non-pharmacological interventions

3.5.1.1. Cognitive behavioral therapy. Evins et al. (2001) concluded that combining bupropion with CBT may facilitate smoking reduction in patients with schizophrenia, as this multimodal intervention was associated with a significantly higher reduction in smoking (6/9 subjects, 66%, $p < 0.001$) comparing to placebo (1/9 subjects, 11%) during the 3-month active treatment period and at the 3-month follow-up (3/9 subjects vs. 1/9 subjects). Regarding smoking abstinence outcomes, one subject in the bupropion group (11%) and no subjects in the placebo group achieved sustained tobacco abstinence at the 3-month follow-up.

Evins et al. (2007) reported a significantly superior effect of bupropion added to short and long-acting NRT and CBT, versus placebo, on 50% to 100% smoking reduction at the end of the treatment (60% vs. 31%; $p = 0.036$) and at 3-month follow-up (32% vs. 8%; $p = 0.039$), as well as on a lower expired air CO at the end of the treatment and at the 3-month follow-up ($F = 13.8$; $p < 0.001$). However, abstinence rates did not differ by treatment group at the end of the treatment (36% vs. 19%), at the 3-month follow-up (20% vs. 8%), and at the 12-month follow-up (12% vs. 8%).

3.5.1.2. Supportive therapy. Weiner et al. (2001) concluded that combining bupropion with supportive group therapy helped patients with schizophrenia decrease their cigarette consumption, although no control group was used in the study. Subjects' mean end expired air CO level decreased over the treatment phase (mean change of 21.06 (SD = 22.25) ($t = -2.68$, $p < 0.05$), but smoking reduction began before bupropion was initiated, which may have been due to the group therapy itself. None of the participants were able to reach smoking abstinence. Weiner et al. (2012) conducted a similar study (combining bupropion with supportive group therapy), but this time a control group was included. There were no significant results favoring bupropion over placebo in this trial regarding smoking outcomes.

3.5.1.3. Contingency management therapy. Tidey et al. (2011) concluded that integrating CM interventions into smoking cessation treatments may help smokers with schizophrenia reduce smoking. The CM intervention reduced cotinine and CO levels by approximately 30% relative to pre-study levels. It was also found that bupropion did not reduce smoking by itself or increase the effectiveness of CM intervention. There was no significant decrease in the cotinine and CO levels in the NR intervention groups.

3.5.2. NRT combined with non-pharmacological interventions

3.5.2.1. Behavioral therapies. Addington et al. (1998) concluded that combining NRT (nicotine patch) with a standard behavioral group

Table 2
Quality assessment of the clinical trials based on the Jadad scale.

References	Described as randomized: yes (+1) no (0)	Method of randomization: appropriate (+1) inappropriate (−1) not described (0)	Described as double-blind: yes (+1) no (0)	Method of double-blinding: appropriate (+1) inappropriate (+1) not described (0)	Description of withdrawals and dropouts: yes (+1) no (0)	Final Jadad score (maximum of 5)
Addington et al., 1998	0	0	0	0	+1	1
Evins et al., 2001	+1	0	+1	0	+1	3
Evins et al., 2007	+1	0	+1	+1	+1	4
George et al., 2000	+1	+1	0	0	+1	3
Tidey et al., 2002	0	0	0	0	+1	1
Tidey et al., 2011	+1	+1	+1	0	+1	4
Weiner et al., 2001	0	0	0	0	+1	1
Weiner et al., 2012	+1	0	+1	0	0	2
Williams et al., 2010	+1	+1	0	0	+1	3

therapy (based on the American Lung Association (ALA) Freedom from Smoking Program) was effective in reducing smoking among individuals with schizophrenia, as a significant number of subjects ($n = 21$, 42%) quitted smoking at the end of the group program. Although this number decreased at both 3-month (16%) and 6-month (12%) follow-ups, it was still significantly different from pre-group assessment.

Williams et al. (2010) found no differences between two behavioral counselling approaches, high-intensity (TANS) versus a low-intensity behavioral counselling program (MM), both combined with NRT (nicotine transdermal patch). Smokers in both groups significantly reduced smoking as measured by cigarettes per day (from 24.6 to 13.1; Wilks' Lambda 0.608, $p < 0.001$) and by expired CO (from 19.0 ppm to 14.5 ppm; Wilks' Lambda 0.865, $p < 0.001$). Twenty-one percent ($n = 18$) of participants had continuous abstinence at 3-month follow-up, and 17% ($n = 15$) at 26 weeks after the target quit date, which were not significantly different between conditions.

George et al. (2000) concluded that two group psychotherapy programs for smoking cessation (ALA group and a manualized and specialized schizophrenia smoking cessation program) combined with NRT (nicotine transdermal patch) did not result in significantly different smoking outcomes. Smoking abstinence did not differ significantly between the ALA group (6/17 subjects, 35.3%) and the specialized group therapy (10/28 subjects, 35.7%) ($\chi^2 = 0.16$, $p = 0.69$). This study also reported a decline in abstinence rates from the end of treatment to the 6-month follow-up.

3.5.2.2. Contingency management therapy. Tidey et al. (2002) examined the effects of CM on cigarette smoking with and without NRT (transdermal nicotine) and found that, during CM conditions, participants provided CO samples below the cutoff on 33% to 40% of occasions over a 5-day period. Thus, CM reduced smoking but NRT did not enhance that effect. These results offer further evidence supporting the effectiveness of CM in reducing smoking among patients with schizophrenia, but higher doses of NRT, or another pharmacotherapy, may be needed to enhance that effect.

3.6. Secondary outcomes (psychiatric symptoms)

All eight studies that included psychiatric symptoms as secondary outcomes did not report adverse effects of non-pharmacological therapies, study medication, or smoking status on psychiatric symptoms and on neuropsychological performance. Evins et al. (2001) concluded that bupropion treatment was associated with an improvement in negative symptoms (although not significantly during the active treatment) and with a greater stability of positive and depressive symptoms during the quit attempt, compared to placebo. In fact, it was found in the same study that psychiatric symptoms increased significantly in the placebo group during active treatment ($F(1,16) = 5.6$, $p = 0.03$) and at follow-up ($F(1,16) = 6.1$, $p = 0.02$), mainly due to changes in positive symptoms of psychosis (hallucinations, delusions, and formal thought disorder) and in depressive symptoms (Evins et al., 2001). In the study conducted by Evins et al. (2007), akathisia and extrapyramidal symptoms slightly decreased in the bupropion group, and increased in the placebo group at the end of the treatment. Tidey et al. (2011) reported a significant decrease in psychiatric symptoms during the study in all intervention conditions.

4. Discussion and conclusions

This systematic review aimed to clarify the effectiveness of multimodal smoking cessation interventions in adult smokers diagnosed with schizophrenia. The selected studies analyzed in this review showed that multimodal smoking cessation interventions can be effective in reducing smoking among patients with schizophrenia. In fact, all studies reported higher biochemically validated smoking reduction rates after treatment, and this effect was maintained at follow-ups in most of them. This conclusion is supported by other studies that also reported the effectiveness of multimodal smoking cessation treatments among patients with stable psychotic disorders (Raich et al., 2018; Stubbs et al., 2015). However, multimodal interventions were not as effective in helping individuals to achieve smoking abstinence and to maintain it over time. The majority of the studies reported low smoking abstinence rates, which progressively decreased over time. According to Mann-Wrobel et al. (2011), individuals with schizophrenia are generally heavy smokers and have multiple failed quit attempts, which may lead to low confidence in one's ability to quit smoking. Another obstacle is related to the fact that tobacco may compensate downregulated dopamine expression and receptors in the brain, with positive effects on motivation, mood and cognition, and on preventing weight gain (Glassman, 1993; Kavanagh et al., 2002; Keltner and Grant, 2006; Lohr and Flynn, 1992). Thus, a better understanding of the comorbidity of schizophrenic illness and nicotine dependence is needed in order to develop effective interventions for both disorders (George et al., 2000; Tidey et al., 2002).

Regarding non-pharmacological interventions, studies analyzed in this review found no differences between high intensity interventions and low intensity interventions, as well as between interventions specialized to individuals diagnosed with schizophrenia and standard community-oriented smoking cessation programs, combined with pharmacotherapy, although all of them facilitated smoking reduction. However, these results are not in line with the literature that states that due to the cognitive, affective, and social deficits associated with schizophrenia, standard programs may not be suitable for this population (Addington et al., 1998). Williams et al. (2010) added that altered learning and information processing in schizophrenia require adaptations from traditional smoking approaches. However, it seemed that group therapy is more effective than individual therapy in smoking cessation programs for patients with schizophrenia, as group therapy enhances role playing and facilitates teamwork, cooperation and creative problem solving (Williams et al., 2010). Thus, it becomes clear that addressing smoking cessation among individuals with schizophrenia is crucial even through brief and non-specialized interventions, as it increases the chances of smoking reduction.

Regarding pharmacological intervention, bupropion combined with non-pharmacological intervention has showed effectiveness in smoking reduction compared to placebo. These results are in line with a Cochrane systematic review which concluded that bupropion was effective at both 3 and 6 months in this population (Tsoi et al., 2013). In the current systematic review, bupropion has showed a superior effect when combined with NRT and CBT (Evins et al., 2007; Evins et al., 2001), but its effectiveness was not so clear when combined with supportive therapy and with CM (Tidey et al., 2011; Weiner et al., 2012). Tidey et al. (2011) suggested that the lower motivation levels of participants could reduce the effectiveness of medication. According to Evins et al. (2007) and George et al. (2000), bupropion may improve abstinence rates the most, among smokers with schizophrenia, when combined with high-dose dual NRT, due to the patients' decreased nicotinic receptor expression and function. In fact, the studies analyzed in this review suggest that smoking cessation rates with NRT are modest in schizophrenia and support offering higher doses of NRT (George et al., 2000; Tidey et al., 2002). Tidey et al. (2002) concluded that combining NRT with CM may not reduce smoking more than CM intervention alone, probably because nicotine patch has not provided a sufficient level of nicotine replacement for participants. It would also be important to analyze, in future studies, the effect of type of antipsychotic (atypical vs. conventional) on abstinence outcomes, since switching from typical to atypical antipsychotics (with no particular atypical antipsychotic showing an advantage) may indirectly decrease cigarette smoking by reducing neuroleptic-induced akathisia (Barnes et al., 2006; McChargue et al., 2002).

An important finding of this review is that multimodal smoking cessation interventions did not worsened psychiatric symptoms. In fact, in some studies, multimodal interventions were associated with better

outcomes regarding akathisia, and stability of psychotic and depressive symptoms. These results are in line with Anthenelli et al. (2016) who stated that varenicline, bupropion and NRT are well tolerated and effective in adults with psychotic, anxiety, and mood disorders. Pearsall et al. (2019) also found that these treatments (varenicline, bupropion and NRT) did not notably affect the physical or mental health of participants with severe mental illness. This finding is particularly important, because despite smoking more than the general population, patients with schizophrenia are rarely encouraged to stop or supported in their efforts to quit smoking, which contributes to nicotine addiction undertreatment in this population (Addington et al., 1998; Weiner et al., 2001). Thus, clinicians should not be concerned of worsening psychiatric symptoms in patients with schizophrenia by recommending multimodal smoking cessation interventions. In fact, multimodal interventions may play an important role in harm reduction, by facilitating smoking reduction while possibly improving stability of psychiatric symptoms during an attempt to quit smoking. Given the continuing high rates of tobacco addiction in this population, there is a need to integrate nicotine dependence pharmacotherapy and psychosocial treatments into mental health treatment settings (Williams et al., 2010). Helping patients with schizophrenia achieve smoking abstinence will improve not only the individuals' health, but also their economic situation, and the implementation of smoke-free settings (Addington et al., 1998).

4.1. Strengths and limitations

This systematic review holds some limitations, such as: the small number of studies included, the high levels of heterogeneity due to different protocols, the variety of measuring instruments used. Some studies included were pilot and non-randomized with no control groups, which lead to difficulties in comparing the data. Some studies did not have a follow-up, which fails to capture longer-term intervention impact. Only published studies were considered for inclusion. Furthermore, most studies were conducted in the USA, and we believe that directly applying the results to other countries could be inappropriate.

There are also a number of strengths. The study was planned according to PRISMA guidelines (Moher et al., 2009); more interventions beyond randomized controlled trials were included in the review to understand the qualitative aspects of interventions that may otherwise have been excluded; most of the studies used biometric measures (exhaled CO or cotinine), increasing the validity of the results.

4.2. Clinical implications

Evidence suggests that multimodal smoking cessation interventions for individuals diagnosed with schizophrenia should be recommended by clinicians, as they are effective in reducing smoking without worsening psychiatric symptoms. Further studies are needed to understand how interventions can become more effective in helping patients achieve long-term smoking abstinence, as there is few current evidence that support this association. A better understanding of factors that lead to successful smoking cessation outcomes in patients with schizophrenia may contribute to improve treatments for this subset of smokers (George et al., 2000).

CRediT authorship contribution statement

All authors have contributed to and approved the final manuscript.

Declaration of competing interest

The authors declare no conflicts of interest.

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