





Effectiveness and Safety Profile of Alternative Tobacco and Nicotine Products for Smoking Reduction and Cessation: A Systematic Review

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Background: Alternative tobacco and nicotine products such as electronic cigarettes (EC), smokeless tobacco, and nicotine replacement therapy (NRT) are currently being assessed as options in tobacco harm reduction due to their potential role in smoking reduction and smoking cessation.

Objective: To provide the current evidence on the effectiveness and safety of various alternative tobacco and nicotine products for smoking reduction and cessation.

Methods: A systematic review using databases from MEDLINE (PubMed), EMBASE, and The Cochrane Library was conducted up to December 2020 to identify eligible experimental and observational studies assessing the use of alternative tobacco and nicotine products on smoking reduction and smoking cessation and the safety of these products. The Cochrane Risk of Bias 2 (RoB 2) and ROBINS-I tools were used to assess the risk of bias of the included studies. Results were described through a narrative synthesis of the evidence.

Results: From 1955 retrieved references, 44 studies (31 randomized controlled trials/RCTs and 13 prospective cohort studies) met the inclusion criteria and were included in the review. Twenty-nine studies were assessing EC, one study evaluated heat-not-burn (HNB) product, five studies were focused on snus, and nine studies assessed NRT in the form of nicotine patch, gum, etc. The overall results suggested that alternative tobacco and nicotine products in the form of EC, snus, and NRT can moderately reduce daily cigarette consumption and has potential to assist smoking cessation attempts, with fewer adverse events.

Conclusion: The findings suggested that alternative tobacco and nicotine products have a potential role in assisting smoking reduction and cessation, highlighting their role in the tobacco harm reduction approach. Further studies should focus on investigating long-term outcomes, safety, and effectiveness of alternative tobacco and nicotine products to better inform smoking reduction/cessation policy.

PROSPERO Registration Number: CRD42020205830.

Keywords: cigarette smoking, smoking cessation, smoking reduction, nicotine, e-cigarettes, snus, nicotine replacement therapy, harm reduction

Background

Smoking is the most significant modifiable risk factor of morbidity and mortality, associated with a wide range of diseases, such as chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), stroke, lung cancer, and other chronic diseases.¹⁻⁴ The prevalence of COPD, in particular, increased with prolonged smoking duration both in men and women.⁵ Smoking-related illnesses are estimated to cause

more than eight million deaths annually, worldwide.⁶ Recent population-based studies showed that prolonged smoking was associated with 10 years reduced life expectancy, and cessation before the age of 40 reduced the risk of smoking-related death by up to 90%.^{7,8} Evidence suggests that approximately half of the smokers reported having made a quit attempt in the past year, but less than 10% of such attempts succeed.^{9,10}

Behavioral approaches such as cognitive behavior therapy, group therapy programs, or individual counseling sessions with or without pharmacotherapy, eg, varenicline, bupropion, etc, have been proven effective for smoking cessation interventions.^{11,12} In patients with COPD, improved lung function and respiratory symptoms were observed in those who received nicotine partial agonist, in addition to individual counseling.^{13,14} However, these interventions have to be delivered by professional facilitators such as physicians, clinical psychologists, nurses, etc.¹² Alternative tobacco and nicotine products such as nicotine replacement therapy (NRTs), electronic nicotine delivery systems (ENDS), electronic cigarette (e-cigarette/EC), and low-nitrosamine smokeless tobacco, are self-help initiated, less invasive interventions that have the potential to assist cessation by attenuating withdrawal symptoms.^{15–18} These adjunct strategies facilitate a transition to abstinence, typically by providing either a markedly lower level or no nicotine, but with much-reduced health risks as a substantially lower amount of harmful chemical constituents are present.^{19,20} Several clinical trials showed that alternative nicotine and tobacco products were more effective for facilitating sustained abstinence and rated significantly more pleasant than other interventions.^{21,22} These harm reduction attempts have the potential to generate tangible public health benefits; nevertheless, this is counterbalanced with concern regarding widespread re-normalization of addiction behavior and its adverse consequences.^{23,24} In a small-scale laboratory-based study, Vardavas et al showed that adverse pulmonary effect was observed following the use of alternative nicotine products.²⁵ Previous studies showed that the alternative tobacco and nicotine products are currently used by 0.5–5% of the adult population,^{26–28} with up to 20% of smokers using these products as reduction/cessation aid.^{29–32} However, there is little clarity regarding the overall effectiveness and safety of the alternative tobacco and nicotine products and their role in smoking reduction and cessation.^{17,33–35}

Assessing the risks and benefits of the alternative tobacco and nicotine products are challenging due to the lack of accurate biomarkers^{36,37} and paucity of evidence in this regard.^{38,39} A comprehensive understanding of the role of

these products is important to better inform tobacco harm reduction policy. Previous systematic reviews have been conducted, but these reviews primarily focused on a single form of alternative tobacco and nicotine products,^{17,23,34,36,38,40} did not investigate the safety,^{41,42} and performed within the context of a single country, limiting its generalizability.⁴³ Thus, this comprehensive systematic review was performed to provide an understanding of the overall effectiveness and safety of the alternative tobacco and nicotine products for smoking reduction and/or cessation.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; [Supplementary materials](#)).⁴⁴ The objectives and methods of this review were registered in the International Prospective Register of Systematic Review (PROSPERO; [Supplementary materials](#)).

Search Strategy

The following databases were used to identify relevant literature, ie, MEDLINE (PubMed), EMBASE, and The Cochrane Library up to December 2020. A systematic search was conducted in these electronic databases to identify relevant studies on the topic of alternative tobacco and nicotine products. The definition of alternative tobacco and nicotine products in this study included heat-not-burn (HNB) products, electronic cigarette (EC), smokeless tobacco such as chewing tobacco, snuff, and snus, and nicotine replacement therapy (NRT) in the form of gum, transdermal patch, nasal spray, oral inhaler, etc.^{45–49} Details on the definition of alternative tobacco and nicotine products are provided in [Supplementary materials Table S1](#).

The following keywords were used for the search: “Electronic Nicotine Delivery Systems” OR “E-Cigarette Vapor” OR “Vaping” OR “e-cigarette” OR “tobacco, smokeless” OR “Tobacco Use Cessation Devices” OR “tobacco, waterpipe” OR “Smoking Water Pipes” AND “drug-related side effects and adverse reactions” OR “Smoking Cessation” OR “Smoking Reduction” (for details on search strategy in all databases see [Supplementary materials Table S1](#)).

Study Selection

The search records from all electronic databases were exported to Mendeley reference manager and checked for duplicates. Screening process was carried out in two

stages, ie, initial screening based on title and abstracts followed by full-text screening. Both screening processes were independently performed by two reviewers (NZ and FVP). Any discrepancies were resolved by consensus or by discussions with a third and fourth reviewer (AAS and WNI). The following inclusion criteria were used for the screening process: published articles were selected if they assessed the utilization of alternative tobacco and nicotine products in terms of smoking reductions and smoking cessation or assessing the safety profile of alternative tobacco and nicotine products in terms of reported clinical-related adverse event or clinical and laboratory-measured adverse events in the adult population, published in the last 10 years. Studies on animals and cells, any protocol articles, conference proceedings, review articles, and non-English studies were excluded in the initial screening process. In the full-text screening, we included both experimental (randomized-controlled trials/RCTs) and observational studies (retrospective/prospective cohort, case-control design and nonintervention arms of randomized controlled trials). Irrelevant studies, cross-sectional, case series, and case reports were excluded.

Data Syntheses and Extraction

From each included study, two reviewers (NZ and FVP) extracted data using a predetermined standardized data extraction form. This form was approved by all authors and amended as required. We extracted data regarding study characteristics (author, year of publication, country, study design, characteristics of participants, number of participants, type of interventions, outcome measure, length of study and funding source), and study design. We also extracted study outcomes in terms of smoking reduction, smoking cessation and adverse events along with its reported effect measures.

Risk of Bias and Quality Assessments

Risk of bias and quality assessments were independently evaluated by two reviewers (NZ and FVP) using The Cochrane Risk of Bias 2 tool (RoB 2) for RCTs, in which each included study was assessed qualitatively using five domains ie, randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.⁵⁰ The overall bias for each study was then classified as high, some concerns or low risk of bias, based on the criteria listed in the RoB 2 detailed guideline.⁵¹ Risk of bias graph was derived from this tool. The ROBINS-I

tool was used for assessing the risk of bias in nonrandomized and observational studies.⁵² The following domains were evaluated, ie confounding, selection of participants, classifications of interventions, deviations from intended intervention, missing data, measurement of outcome and selection of reported results. The overall risk of bias from these domains was qualitatively categorized as critical, serious, moderate or low risk of bias, based on the criteria explained in the ROBINS-I detailed guideline.⁵³

Results

Systematic Search

The initial search retrieved 1955 records in PubMed, Embase and the Cochrane Library. After removing 363 duplicates, 1592 articles were screened by title and abstract, excluding 889 records. After the full text screening on 703 articles, 43 articles were included in the systematic review (Figure 1). One extra relevant study⁵⁴ was identified from the included references, resulting in the final inclusion of 44 studies.

In terms of study design, 31 studies were RCTs (experimental) and the remaining 13 studies were prospective cohort studies (observational). Based on criteria of alternative tobacco and nicotine products explained previously in the methods, 29 included articles were assessing EC,^{22,55–82} in which 16 articles were RCTs,^{22,55–69} and 13 studies were prospective cohort studies,^{70–82} one RCT assessing HNB products,⁸³ five RCTs assessing snus (categorized as smokeless tobacco)^{18,54,84–86} and nine RCTs focusing on NRT (eg, nicotine patch, gum, etc).^{87–95} We did not find any observational studies in categories other than EC products.

Characteristics of Included Studies

The general characteristics and study outcomes of included studies are provided in Table 1. The majority of the studies were assessing EC (68%), followed by NRT (21%), smokeless tobacco (9%) and HNB products (2%). Most of the included studies were carried out in high-income countries, such as the USA (20/43), Italy (7/43) and the UK (5/43). The length of included RCTs varied, from days, weeks, to one year. Details on the outcomes in smoking reduction, smoking cessation and adverse events of the included studies are summarized in [Supplementary materials, Table S1](#)

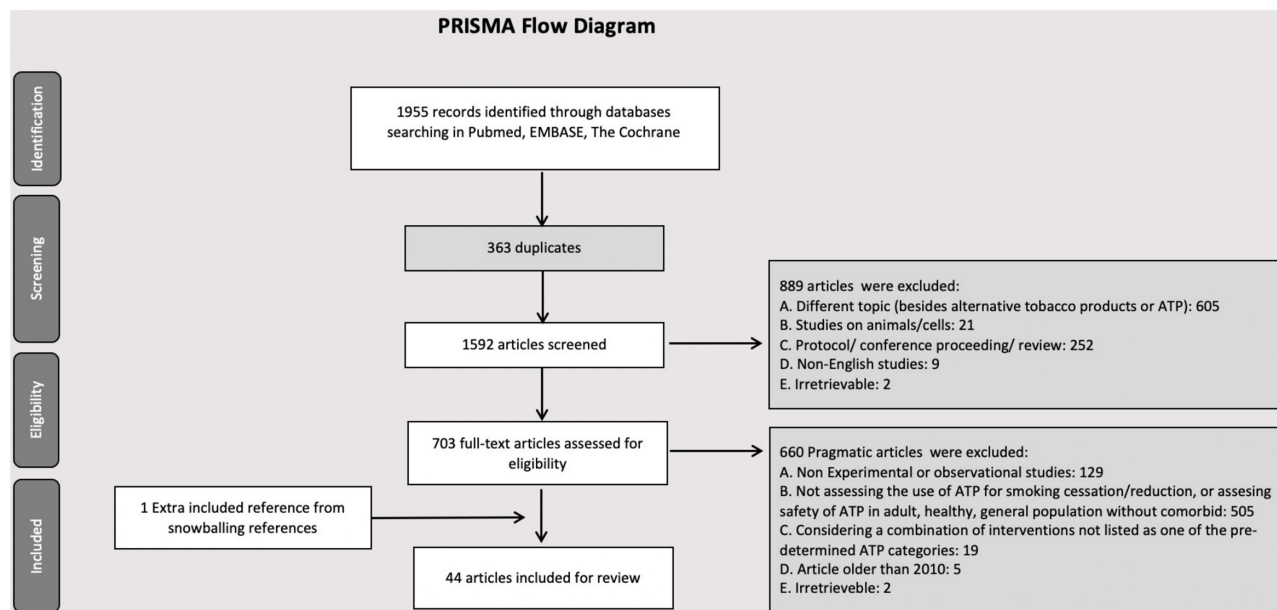


Figure 1 PRISMA flow diagram of study selection.

Notes:PRISMA figure adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.⁴⁴ © 2009 Moher et al. Creative Commons Attribution License.

Smoking Reduction

There were nine RCTs^{22,55–57,59,63,66,68,69} and nine prospective cohort studies^{70–74,78,80–82} in the EC group, four RCTs on snus^{18,54,85,86} and two RCTs on NRT^{87,91} which evaluated the effect of alternative tobacco and nicotine products in smoking reduction. Although variation in number of participants and length of the study was observed between included RCTs in the EC group, all studies reported moderately smoking reduction among trial participants, in which five studies^{22,55,57,63,69} reported approximately 50% or more reduction in the number of cigarette consumption per day. In addition, three studies reported a greater reduction in nicotine EC compared to non-nicotine EC.^{63,66,69} Results from cohort studies suggested a similar trend, that the use of EC resulted in a considerably decreased number of cigarettes per day,^{71–74,80–82} and that EC use was associated with higher odds of reduced daily cigarette consumption.^{70,74} Nevertheless, contradictory results were also observed among studies, as two studies argued that EC might decrease the likelihood of lowering cigarette consumption.^{70,78}

Studies on the use of snus for smoking reduction suggested that snus can lead to a decline in number of cigarettes used per day, although the observed reductions were moderate, approximately in a range of 20–30%.^{18,85,86} In addition, one study that defined their primary endpoint as smoking reduction $\geq 50\%$ suggested that there was no

statistically significant difference between snus and the placebo group, although the proportion of participants that reported more than 75% reduction was significantly higher in the snus group.⁵⁴ Two out of four included RCTs on snus suggested that snus may be inefficient as a harm reduction approach compared to another type of alternative tobacco and nicotine products, ie nicotine gum,⁸⁶ and that provision of snus did not increase smoking abstinence.¹⁸ Furthermore, that RCTs that focused on NRT in the form of nicotine gum and transdermal nicotine patches also reported a moderate reduction in cigarette consumption.^{87,91}

Smoking Cessation

In terms of smoking cessation, seven included RCTs^{22,55–57,59,66,69} and all included prospective cohort studies^{70–82} assessing EC were observing the quit attempts among participants. Due to variation in the length of the study, the definition of smoking cessation was also varied between studies. All seven RCTs had a long duration of observation, and smoking abstinence was observed in a prolonged manner, ie, continuous abstinence ranging from six months to one year. Overall, the results from seven RCTs in the EC group suggested a very modest portion of subjects who were abstinent from cigarette smoking.^{22,55–57,59,66,69} The results from cohort studies showed conflicting results with regard to smoking cessation. Ten cohort studies indicated that the use of EC was associated

Table 1 General Characteristics of Included Studies

Author, Year of Publication	Country	Participants		Type of Intervention(s)	Main Outcomes			Length of Study	Overall Risk of Bias ^a	Funding ^b	
		Characteristics	Number		Smoking Reduction	Smoking Cessation	Adverse Events				
Experimental; RCT											
Heat-not-burn Product											
Haziza et al 2016 ⁸³	Switzerland	21–65 years old; smoke ≥10 commercially available non-menthol cigarettes per day for ≥3 consecutive years	160	THS 2.2	–	–	✓	The incidence of AE in THS group is lower than cigarettes group. Oropharyngeal pain and vertigo percentage is higher in THS groups	5 days	Some concerns	Sponsored
Electronic Cigarettes (EC)											
Bullen et al 2013 ⁵⁵	New Zealand	≥18 years old; smoke ≥10 cigarettes per day for the past year	657	EC, nicotine patches or non-nicotine EC	✓	✓	✓	EC, with or without nicotine were modestly effective for smoking cessation, and few AEs	6 months	Low	Nonprofit
Caponnetto et al 2013 ⁵⁶	Italy	≥18 years old; smoke ≥10 factory made cigarettes per day, for at least the past 5 years	300	Group A (12 weeks of 7.2 mg EC), group B (6-weeks of 7.2 mg EC and 6 weeks with 5.4 mg EC), and group C (12 weeks of non-nicotine EC)	✓	✓	✓	EC, with or without nicotine decreased cigarette consumption without any significant reported AEs	1 year	Low	Sponsored
Adriaens et al 2014 ⁵⁷	Belgium	Mean age 43.71 years old; smoke ≥10 cigarettes per day for at least 3 years	48	Two different ECs (EC1 and EC2) as experimental groups and control groups (cigarettes). After 8 weeks, the control group are allowed to smoke EC	✓	✓	–	EC was considered effective for smoking reduction and smoking cessation	32 weeks	Some concerns	N/A
D’Ruiz et al 2015 ⁵⁸	USA	21–65 years old; smoke an average of ≥10 manufactured cigarettes per day for at least 12 months	24	Five different types of classic and flavored EC (product A-E) or product F: cigarettes	–	–	✓	The use of EC is considered tolerable	11 Days	Some concerns	Sponsored

(Continued)

Table 1 (Continued).

Author, Year of Publication	Country	Participants		Type of Intervention(s)	Main Outcomes			Main Conclusion	Length of Study	Overall Risk of Bias ^a	Funding ^b
		Characteristics	Number		Smoking Reduction	Smoking Cessation	Adverse Events				
Cibella et al 2016 ⁵⁹	Italy	≥ 18 years old; smoke ≥ 10 tobacco cigarettes per day for at least the past 5 years	183	Group A: 12 weeks EC 2.4%; Group B: 6 weeks EC 2.4% and 6 weeks EC 1.8%; Group C: 12 weeks non-nicotine EC	✓	✓	✓	Smoking reduction and cessation is considered moderate. The EC is well tolerable	1 year	Some concerns	Sponsored
Cravo et al 2016 ⁶⁰	UK	21–65 years old; BMI 18–35 kg/m ² ; smoke 5–30 cigarettes per day for at least one year	387	Switching to using an EVP prototype or continuing to smoke their own cigarettes brand for a total of 12 weeks	–	–	✓	More participants in the EVP group experienced AEs	12 weeks	Some concerns	Sponsored
Farsalinos et al 2016 ⁶¹	Italy	≥ 18 years old; smoke ≥ 10 tobacco cigarettes per day for at least the past 5 years	300	2.4% EC, or 1.8% EC or non-nicotine EC	–	–	✓	Quitters group showed the highest reduction of systolic BP. Diastolic BP also significantly reduced	1 year	Low	Sponsored
Kumral et al 2016 ⁶²	Turkey	≥ 18 years old; Smoke one pack of cigarettes per day for at least 5 years	98	Smokers using EC to quit (EC group); Group 2: Smokers who quit smoking without the aid of medical therapy and a device (non-EC group)	–	–	✓	Sinonasal symptoms were better after 3 months of cessation of cigarette smoking	3 months	Some concerns	N/A
Tseng et al 2016 ⁶³	USA	21–35 years old; daily smoker; smoke ≅ 10 cigarettes per day	99	Disposable 4.5% EC or non-nicotine EC for 3 weeks	✓	–	✓	Using EC increases the odds of CPD reduction by 50% without any significant reported AEs	3 weeks	Low	Nonprofit
Walele et al 2016 ⁶⁴	UK	21–65 years old; BMI 18–35 kg/m ² ; smoke 5–30 cigarettes per day for at least one year	24	Part 1: 4 groups consist of different doses of EC, NRT nicotine inhalator and cigarettes Part 2: 4 groups with different doses of EC	–	–	✓	The highest nicotine concentration EC has more frequent AEs	1 week	Some concerns	Sponsored

D'Ruiz et al 2017 ⁶⁵	USA	21–65 years old; smoke ≥10 manufactured tobacco cigarettes per day	105	Different types of rechargeable EC (Group A1-A3); different types of rechargeable and disposable EC + usual brand cigarettes (Group B1-B3); or complete tobacco and nicotine product cessation (group C)	-	-	✓	✓	Exclusive use of EC reduces more number of CPD than dual users. EC is considered effective as a cessation method	1 week	Some concerns	Sponsored
Baldassarri et al 2018 ⁶⁶	USA	≥18 years old; smoke 1 or more tobacco cigarettes per day	40	Both groups received standard care (nicotine patch and counselling) and were randomized to: EC or non-nicotine EC	✓	✓	✓	✓	There is no significant difference in cigarette consumption reduction and AEs among both groups, and only a small portion of subjects abstinent from smoking	24 weeks	Some concerns	Nonprofit
George et al 2019 ⁶⁷	UK	≥18 years old; smoke ≥15 cigarettes per day for at least 2 years	114	Group 1: EC containing 16 mg nicotine; Group 2: non-nicotine EC plus nicotine flavoring; Group 3: unwilling to quit continued with cigarettes in a parallel preference arm	-	-	✓	✓	Switching to EC improves FMD and vascular endothelial function significantly	1 month	Some concerns	Nonprofit
Hajek et al 2019 ²²	UK	≥18 years old; smoke tobacco cigarettes (amount not specified)	886	Nicotine-replacement products or EC (18 mg/mL)	✓	✓	✓	✓	EC is more effective in reducing cigarette consumption than NRT. More AEs experienced in the EC group	1 year	Some concerns	Nonprofit
Veldheer et al 2019 ⁶⁸	USA	21–65 years old; smoke ≥10 cigarettes per day	520	Cigsab (a non-aerosol producing, non-nicotine containing cigarette substitute) or EC (with 0, 8, or 36 mg/mL nicotine concentration)	✓	-	-	-	EC is more effective in reducing cigarette consumption than cigsab	9 months	Some concerns	Nonprofit
Walker et al 2020 ⁶⁹	New Zealand	≥18 years old; smoke tobacco cigarettes (amount not specified)	1124	Patches (21 mg, 24h); patches plus EC (18 mg/L), or patches plus a non-nicotine EC	✓	✓	✓	✓	Similar percentage on cigarette reduction in both groups, the patches + EC group is significantly higher in continuous abstinence	6 months	High	Nonprofit

(Continued)

Table 1 (Continued).

Author, Year of Publication	Country	Participants		Type of Intervention(s)	Main Outcomes			Main Conclusion	Length of Study	Overall Risk of Bias ^a	Funding ^b
		Characteristics	Number		Smoking Reduction	Smoking Cessation	Adverse Events				
Snus (Smokeless Tobacco)											
Joksić et al 2011 ⁵⁴	Serbia	20–65 years old; smoke >10 cigarettes per day for >1 year	319	Snus (0.5 or 1.0 g) or placebo	✓	✓	✓	Snus was more likely to help smoking cessation than placebo. Significantly more people in snus group were reporting smoking reduction. Overall, the snus was well-tolerated	48 weeks	Low	Sponsored
Fagerstrom et al 2012 ⁸⁴	USA	25–65 years old; smoke daily for at least a year	250	Snus (0.5 or 1.0 g) or placebo	–	✓	✓	Snus is efficient to achieve continuous smoking abstinence. Treatment-related AEs are more frequently reported in the snus group	28 weeks	Low	Sponsored
Burris et al 2014 ⁸⁵	USA	18–65 years old; smoke ≥10 cigarettes per day on average for at least 1 year	57	(1) Cigarettes, (2) Snus to cope or (3) Snus to reduce	✓	–	✓	Snus declined the number of cigarette consumption with mostly mild AEs	2 weeks	Some concerns	Nonprofit
Allen et al 2016 ⁸⁶	USA	18–70 years old; smoke ≥10 cigarettes per day	391	Snus (2.5 mg or 2.6 mg) nicotine/pouch or 4 mg nicotine gum	✓	✓	✓	Women were more likely than men to report AEs during the study. Snus may not be an optimal harm reduction approach for either gender	1 year	High	Nonprofit
Carpenter et al 2017 ¹⁸	USA	≥19 years old; smoke ≥10 cigarettes per day	1236	Six-week supply of snus or not received snus	✓	✓	✓	There is no significant difference in cigarette reduction among both groups, but snus users are less likely to quit cigarettes	58 weeks	Some concerns	Nonprofit

Nicotine Replacement Therapy (NRT)											
Carpenter and Gray 2010 ⁸⁷	USA	18–65 years old; smoke ≥10 cigarettes per day on average for at least 1 year	31	PREP Group: different brand of tobacco lozenges; Control Group: cigarettes	✓	–	✓	Nicotine gum is moderately efficient in reducing cigarette consumption. Mild AEs are more commonly experienced by PREP group	2 weeks	Some concerns	Nonprofit
Carpenter et al 2011 ⁸⁸	USA	≥18 years old; smoke at least 10 cigarettes per day	849	PQA alone or NRT sampling within the context of a PQA	–	✓	–	Nicotine therapy did not give a synergic effect to practice quit attempt (PQA)	6 weeks	Some concerns	Nonprofit
Tennesen et al 2012 ⁸⁹	Denmark and Germany	≥18 years old; smoke cigarettes daily for the last 3 years or more (no lower limit of cigarettes)	479	NMS or placebo spray	–	✓	✓	NMS has a higher continuous abstinence rate than placebo. However, it may increase body weight. The incidence of AEs and SAEs caes is higher in NMS subjects	1 year	Some concerns	N/A
Buller et al 2014 ⁹⁰	USA	18–30 years old. Smoke at least 1 cigarette in the past 30 days	3094	Randomized to one of three cessation services. Smokers could request a free two-week course of nicotine patches	–	✓	–	NRT use helps smoking cessation and achieve continuous abstinence	26 weeks	Some concerns	Nonprofit
Schnoll et al 2015 ⁹¹	USA	≥18 years old; smoke at least 10 cigarettes per day	525	8 (standard), 24 (extended), or 52 weeks (maintenance) of transdermal nicotine patches 21 mg	✓	✓	✓	Long-term use of NRT reduces more cigarette consumption but not increases the odds of abstinence. The long-term use of NRT is well tolerated	1 year	Some concerns	Nonprofit
Caldwell et al 2016 ⁹²	New Zealand	18–70 years old; smoke at least 9 cigarettes per day	502	Active inhaler or placebo inhaler. Subjects from both groups received active nicotine patches 21 mg/24 h for 18 weeks, 14 mg/24 h for 2 weeks, and 7 mg/24 h for 2 weeks.	–	✓	✓	Combined NRT use (inhaler and patch) increases the likelihood to be abstinent. The AE of inhaler and patch are experienced by most subjects in both groups. However the most common side effect in the combined group is progressively declining over time	6 months	Low concerns	Nonprofit

(Continued)

Table 1 (Continued).

Author, Year of Publication	Country	Participants		Type of Intervention(s)	Main Outcomes			Main Conclusion	Length of Study	Overall Risk of Bias ^a	Funding ^b
		Characteristics	Number		Smoking Reduction	Smoking Cessation	Adverse Events				
Schlam et al 2018 ⁸³	USA	≥ 18 years old; smoke ≥ 5 cigarettes per day over the past 6 months	513	(1) medication adherence counselling vs none; (2) automated medication adherence calls vs none; (3) electronic medication monitoring with feedback and counselling vs e-monitoring alone; (4) 26 vs 8 weeks of nicotine patch plus nicotine gum; and (5) maintenance counselling vs none	-	✓	✓	The percentage of days participants used the patch and the number of nicotine gum used were associated with abstinence	1 year	Some concerns	Nonprofit
Preloading Investigators 2018 ⁸⁴	UK	≥ 18 years old; regularly smoke cigarettes, cigars, or roll-up tobacco cigarettes	1792	Preloading arm: nicotine patches 21 mg/24 h; control: not receive nicotine patches	-	✓	✓	Nicotine patch use before quitting has bigger odds on abstinence. There is one case of SAE that is possibly due to nicotine patch use, which is acute coronary syndrome in 64 year old woman	1 year	Some concerns	Nonprofit
Leung et al 2019 ⁸⁵	Hong Kong	≥ 18 years old; smoke ≥ 10 cigarettes per day for at least 1 year	560	Combined NRT group received counselling and nicotine patches and gum (2 mg). Single NRT group received counselling and a nicotine patches	-	✓	✓	Smoking abstinence rate is higher i combined NRT use with small number of AE and non-significant difference between groups	1 year	Some concerns	N/A
Observational; Prospective cohort											
Electronic Cigarettes (EC)											
Polosa et al 2011 ⁸²	Italy	18–60 years old, smoke ≥ 15 factory-made cigarettes per day	40	EC users (a full 4-weeks supply of 7.4 mg EC) and were followed up prospectively for 6 months	✓	✓	✓	EC can significantly reduce the number of CPD. The AEs is waning eventually	6 months	Serious concerns	Sponsored

Polosa et al 2014 ⁸¹	Italy	18–60 years old, smoking ≥15 factory-made cigarettes per day for at least the past 10 years	40	EC users for a period of 6 months and followed up prospectively for 2 years	✓	✓	✓	✓	EC can significantly reduce the number of CPD. The AE is waning eventually. Dizziness and nausea persist for quite a long time	2 years	Serious	Sponsored
Polosa et al 2014 ⁸⁰	Italy	18–60 years old, smoke ≥15 factory-made cigarettes per day for at least the past 10 years	50	EC users and followed-up for 6 months prospectively	✓	✓	✓	✓	Personal vapor can significantly reduce the number of CPD and the AE is waning eventually	6 months	Serious	Sponsored
Al-Delaimy et al 2015 ⁷⁰	USA	18–59 years, had smoked at least 100 cigarettes during their lifetime	1000	Surveyed California smokers at 2 time points 1 year apart	✓	✓	–	–	EC use is decreasing the likelihood to lower cigarettes consumption and achieve abstinence	1 year	Moderate	N/A
Rahman et al 2016 ⁷⁹	Malaysia	18–65 years old; use e-cig alone or with tobacco cigarette for last 1 month	220	(1) single user EC and (2) dual user (EC+cigarettes)	–	✓	✓	✓	EC use is very helpful for smoking cessation. The strongest AE was dry mouth, vomiting, and fever.	1 month	Serious	N/A
Shi et al 2016 ⁷⁸	USA	≥18 years old	2454	A representative cohort of US smokers from the 2010 Tobacco Use Supplement to the Current Population Survey (TUS-CPS) was re-interviewed 1 year later	✓	✓	–	–	Ever use of EC is associated with lower success rate to quit	1 year	Serious	Nonprofit
Mantey et al 2017 ⁷⁷	USA	18–29 years old, current/former cigarette smokers	627	The use of EC by current and former cigarettes smoker	–	✓	–	–	EC use increases the odds to abstain from cigarettes	1 year	Moderate	Non-profit
Mohamed et al 2018 ⁷⁶	Malaysia	≥18–65 years old; existing sole EC and dual users using ECs for at least 1 month	218	24-week observational study of sole EC and dual user using EC for at least 1 month	–	✓	✓	✓	Single user EC has a higher abstinence rate. Dual users have experienced more AEs	6 months	Serious	N/A
Weaver et al 2018 ⁷⁵	USA	≥18 years old; current and established smokers	1284	Survey of established smokers at baseline for a 12-month follow-up study on their smoking and EC use	–	✓	–	–	Any use of EC decrease the likelihood of smoking cessation	1 year	Moderate	Nonprofit

(Continued)

Table 1 (Continued).

Author, Year of Publication	Country	Participants		Type of Intervention(s)	Main Outcomes			Length of Study	Overall Risk of Bias ^a	Funding ^b	
		Characteristics	Number		Smoking Reduction	Smoking Cessation	Adverse Events				
Berry et al 2019 ⁷⁴	USA	≥25 years old, smoke tobacco cigarettes	5124	Data from Population Assessment of Tobacco and Health (PATH) study to investigate the associations between EC initiation and cigarettes cessation/reduction	✓	✓	–	Smokers who initiated daily EC smoking has higher odds of quitting smoking	1 year	Serious	Nonprofit
Flacco et al 2019 ⁷³	Italy	30–75 years old; smoke ≥1 tobacco (only) cigarette daily for ≥6 months (tobacco smokers); users of any type of e-cig for ≥6 months (e-cig users); users of both tobacco and e-cig for ≥6 months (dual users)	915	4-years EC use follow-up of cigarettes user, EC user, and dual user	✓	✓	–	Dual user: decrease the cigarette consumption but did not increase the likelihood of smoking cessation or reduction	48 months	Moderate	Nonprofit
Gomajee et al 2019 ⁷²	France	Adult smokers (mean age 44.9) and former smokers (mean age 43.6)	7425	The use of EC by current and former smokers from the CONSTANCES cohort participants, and who had at least 1 completed follow-up questionnaire	✓	✓	–	EC smokers reduce cigarette consumption significantly and EC use longer than 1 year has a higher chance of quitting smoking	1 year	Moderate	Nonprofit
Sweet et al 2019 ⁷¹	USA	≥18 years; responded as “daily” or “some days/week” use of tobacco cigarettes, smokeless tobacco, e-cigarettes, or dual use of two or more products	617	Participants enrolled in the Tobacco User Adult Cohort and categorized as dual user (daily user of cigarettes and daily or some days per week use of EC). Participants were interviewed face-to-face every 6 months, through 18 months	2713	✓	–	No significant difference in cigarette consumption reduction. Dual users have higher odds in quitting at 6 months	18 months	Moderate	Nonprofit

Notes: ^aOverall bias for RCTs (experimental) were assessed using Cochrane Risk of Bias 2 tool (RoB 2), while observational studies were assessed using ROBINS-1 tools; ^bSponsored: the study was funded by a profit organization; Nonprofit, the study was funded by a nonprofit organization; N/A, the study did not report funding.

Abbreviations: RCT, randomized controlled trial; THS, tobacco heating system; AEs, adverse events; SAEs, serious adverse events; EYP, electronic vapor product; BP, blood pressure; MCC, mucociliary clearance; FMD, flow-mediated dilation; EC, e-cigarette; NRT, nicotine replacement therapy; CPD, cigarette per day; POA, practice quit attempt; NMS, nicotine metered spray.

with a higher likelihood of smoking abstinence and that EC increased the odds to abstain from cigarettes,^{71–74,76,77,79–82} while three cohort studies suggested that any EC users may be at increased risk for smoking cessation failure and that the use of EC was associated with lower success rate to quit smoking,^{70,75,78} with reported adjusted odds ratio (aOR) 0.41; 95% confidence interval (CI): 0.186–0.93,⁷⁰ aOR 0.4, 95%CI: 0.2–0.8⁷⁸ and aOR 0.25, 95%CI (0.11–0.57).⁷⁵ In addition, three studies showed that single user EC had much higher odds to abstain from cigarette consumption than dual users (EC+ cigarette).^{73,76,79} In addition, there was variation in the length of observed abstinence among the included prospective cohort studies, ranging from seven days to 12 months follow-up.

Studies on snus as a smoking cessation method were also unequivocal in their conclusion of whether snus can be an efficient harm reduction approach. Two studies showed that snus was approximately two to three times more efficient in attaining continuous abstinence compared to placebo^{54,84} while two other studies suggested that snus could reduce the likelihood to quit smoking and that snus may not be an ideal way in reducing tobacco harm.^{18,86} Moreover, overall NRT use showed that they helped in sustaining smoking abstinence and that two studies^{92,95} observed a synergetic effect of NRT combination in abstinence rate. More details on study outcomes, including length of abstinence in each study, are provided in [Table S1](#).

Adverse Events

Adverse events were either self-reported or laboratory-measured. Almost all RCTs studies in the EC group were assessing its potential adverse events (14 out of 16 studies).^{22,55,56,58–67,69} In addition, five out of 13 prospective cohort studies on EC also reported adverse events.^{76,79–82} The most frequently reported adverse events in the EC group were classified as mild, such as cough, mouth, and throat irritation, headache, difficulty sleeping, and abnormal dreams. Two studies reported the incidence rate of adverse events of nicotine EC compared to nicotine patches (1.05, 95%CI: 0.82–1.34)⁵⁵ and incidence rate associated with the use of EC (1.60, 95%CI: 1.55–1.65).⁶⁰ Overall results indicated no significant intervention-related severe adverse events. Similar results were also observed in EC cohort studies, that the most frequently reported adverse events were moderate eg, mouth and throat-related problems. The only included HNB study reported the safety profile of tobacco heating system (THS) and indicated only moderate adverse events as

well, for instance, headache, oropharyngeal pain, and abnormal spirometry, with the estimated incidence of 62.5% in THS and 70.7% in the cigarette group.⁸³ Moreover, all studies assessing snus reported intervention-related adverse events. Four studies comparing smokers who were randomized to use snus and no snus (identified as control or placebo) showed that the adverse events were more frequently reported in the snus group compared to the control group.^{18,54,84,85} The adverse events were mostly considered mild eg, nausea, burning in throat, and mouth, and stomach problems. One study assessed the use of snus vs nicotine gum for different gender showed that women were more likely to inform adverse events during the study than men.⁸⁶

In addition, three NRT studies that assessed the use of tobacco lozenges,⁸⁷ nicotine metered spray,⁸⁹ and nicotine patches⁹⁴ described that the adverse events were more common in the intervention group rather than in the control or placebo group. The reported adverse events were mostly mild, however one study suggested the occurrence of severe adverse events ie, acute coronary syndrome, which was possibly related to the use of nicotine patches.⁹⁴ The remaining studies on NRT suggested rather moderate adverse events.^{91–93,95}

Risk of Bias and Quality Assessment

Across the 44 articles included in this review, 31 studies were RCTs. According to study design classification in the RoB 2 tool, 29 studies^{18,22,54–57,59–63,65–69,83–95} were classified as parallel-group trials and the remaining two were categorized as crossover trials.^{58,64} Based on RoB tool assessment, 22 studies out of 31 included RCTs (71%) had some risk of bias, two studies had high risk of bias (6%) and seven studies were deemed low in their risk of bias assessment (23%). In details, 96% of studies had low risk through a selection of the reported result, 96% studies had low risk from measurement of the outcome, 78% had low risk of bias from missing outcome data, 70% were assessed as had a low risk of bias through deviations from intended interventions, and 44% studies had low risk of bias from randomization process. [Figure 2](#) depicts the risk of bias assessment in these 30 included RCTs.

According to ROBINS-I tool to assess the risk of bias in the included observational studies, seven out of 13 studies (54%) had serious risk of bias and six studies had moderate risk of bias (46%). The overall risk of bias assessment from RoB 2 and ROBINS-I can be seen in [Table 1](#).

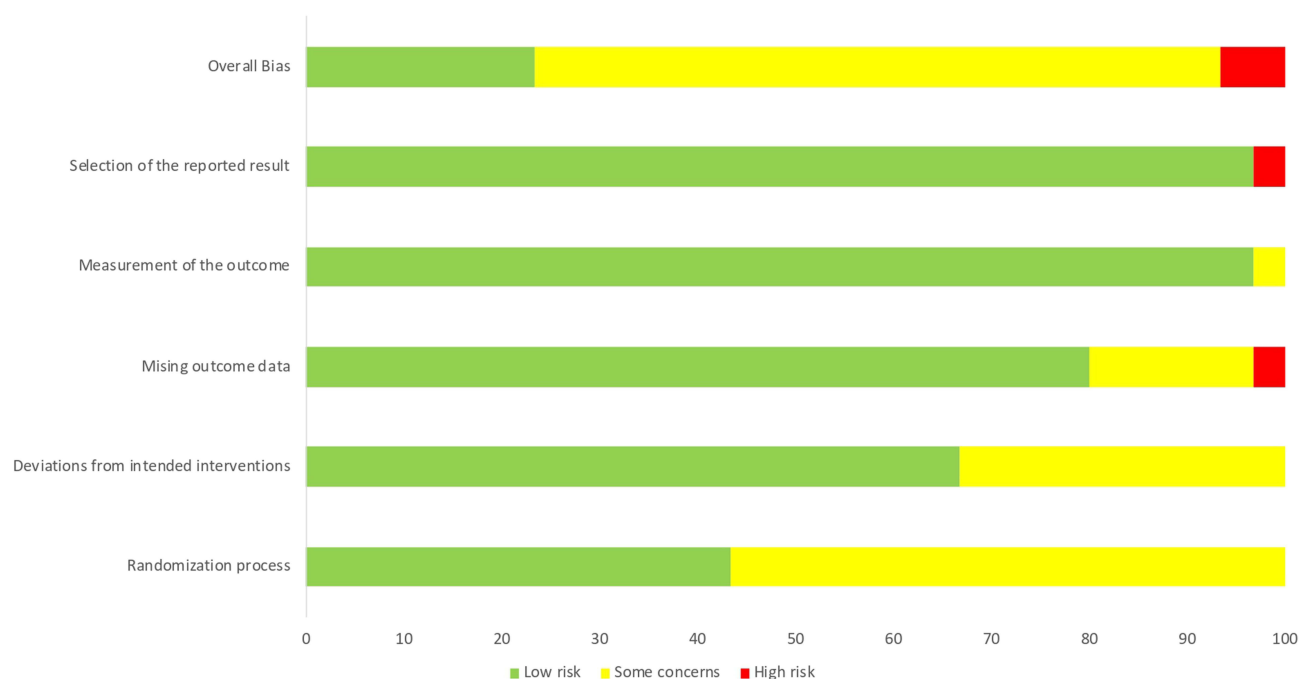


Figure 2 Risk-of-bias assessment of 31 randomized controlled trials in the included studies.

Discussion

This systematic review described the utilization of alternative tobacco and nicotine products in terms of assisting current cigarette smokers in reducing their daily cigarette consumption, and smoking cessation by tempering withdrawal symptoms. This review also defined the potential adverse events that could occur due to using different types of alternative tobacco and nicotine products. Overall, the results indicated that the use of alternative tobacco and nicotine products had the potential to encourage smoking reduction by decreasing the number of cigarettes the current smokers used, even though variations in the efficacy of different products were observed. EC with or without nicotine, snus, and NRT were observed to have a moderate effect in the smoking reduction.^{18,22,55–57,59,63,66,68–74,78,80–82,85–87,91} Moreover, the effectiveness of alternative tobacco and nicotine products on smoking cessation was consistently observed in almost all included experimental and observational studies, even though the abstinence verification method and the degree of effectiveness were varied among different products. Even if the effectiveness is considered moderate, the use of these products was observed to associate with a reduction in the number of cigarettes used, which is prominent in highlighting the substantial evidence demonstrating that gradual reduction in cigarette consumption could further initiate future quit attempts.³⁸

Among all alternative tobacco and nicotine products, EC was the most frequently examined product to aid reduction/cessation among the included studies ($n=18/44$). In addition to helping relieve nicotine withdrawal similar to other interventions, EC use was regarded as an effective behavioral substitute, as it addressed additional sensory and behavioral cues of smoking.^{35,55} The existing literature suggested that EC might be helpful in reduction/cessation attempts, with several RCTs consistently reporting EC as superior compared to the NRT.^{22,55} Another recent trial conducted in the context of the stop smoking service in England further demonstrated that using EC as a cessation aid was likely to be cost-effective compared to NRT in the same setting. It generated a significantly higher one-year quit rate and incurred lower costs than NRT.⁹⁶ Further studies comparing clinical efficacy, as well as the economic benefits of these interventions, are required to determine the generalizability of this finding.

Similar to previous reviews, we found that short to medium-term use of EC was associated with few adverse events, of which the large majority were considered non-serious.^{17,38,58,60,63–66,76} The longest follow-up period was observed in a study by Polosa et al, showing that EC was well-tolerated during six-months use with no major adverse event (requiring hospitalization/unscheduled primary care consultation) occurring during the two-year

follow-up period.⁸¹ In addition, potential pulmonary and cardiovascular benefit was observed in a study where cigarette smokers changed partly or completely to EC for five days,⁶⁵ suggesting potential for harm reduction. Nevertheless, clinical evidence on long-term impact has yet to be characterized. Several studies have shown that toxicants generated from filler (eg, glycerol, polyglycerol) and nicotine inhalation in ECs might contain carcinogens, oxidants, and irritants, such as formaldehyde, acetaldehyde, methylglyoxal, and acrolein,^{97,98} and its chronic exposure has been associated with inflammation.⁹⁹ Yet, previous study showed that compared with combustible tobacco products, ECs contain a significantly lower level of toxicants.¹⁰⁰ Understanding whether lower exposure to these toxicants will result in tangible long-term health benefit/harm is urgently required.

Although the findings from this review indicated that ECs might be one of the potential strategies in tobacco harm reduction, it should be emphasized that since EC products were very diverse in both design and characteristics, the effectiveness and safety might differ as well. Exposure to nicotine and other potentially toxic substances in ECs was varied and depended largely on product characteristics, such as liquid constituents, device characteristics, and settings.^{101,102} In addition, the risk of smoking relapse in a former smoker using ECs remains unclear. The most recent systematic review and meta-analysis study showed an increased risk of smoking relapse among EC users (RR 1.38 (95%CI: 1.11–1.65)). However, this pooled estimate was based on very few studies (three studies in the quantitative analysis).¹⁰³ Therefore, more studies are needed to further confirm this finding.

Besides, the included studies primarily focused on the potential effectiveness of ECs for smoking reduction and cessation in adult smokers, when in reality, these products were also being used by youth, possibly those who had never tried cigarettes.¹⁰² There are also increasing public health concerns that ECs may renormalize “smoking-like” behavior, particularly among youth. The prevalence of EC use among adolescent populations is currently increasing, posing a concern whether ECs are exposing this vulnerable group to nicotine. Although there is evidence that ECs are considered safer in comparison to cigarettes, the early exposure to nicotine may predict concerning patterns of future nicotine use. In addition, there have been reports of pulmonary risks such as the condition electronic-cigarette-associated lung injury (EVALI) and neurodevelopmental effects.¹⁰⁴ Furthermore, very little evidence

existed on EC as a smoking cessation approach among youth.¹⁰⁵

In order to assess EC as one of the tobacco harm reduction approaches at a population level, a thorough understanding of the estimation of both potential benefits and harms from EC should also be taken into account. In addition, the huge variation in terms of length of studies and the number of participants in the included studies in this review suggested that more well-designed RCTs and observational studies are needed to further clarify our findings.

Studies on the use of snus for smoking reduction were not unequivocal in their conclusion whether snus can be an efficient smoking reduction/cessation approach.^{18,85,86} In one of the largest trials involving 1236 participants that reported snus decreased quit attempts, the provision of snus was unguided without any additional support.¹⁸ The importance of behavioral support as an adjunct for smoking reduction/cessation programs has been underlined by a previous Cochrane review by Hartmann-Boyce et al.¹⁰⁶ This review showed high-certainty evidence that provision of behavioral support (eg, group therapy/individual counseling, either in-person or by telephone; written material), in addition to pharmacotherapy was likely to increase quit attempts by up to 20%, based on pooled estimates from 65 trials.^{106,107}

Previous meta analysis comprising two RCTs investigating effectiveness of snus showed that snus increased quit rates.¹⁰⁸ Nevertheless, both trials had relatively small sample sizes (n=250 and 319), and both success rates were relatively low.^{54,64} Snus had been reported as the preferred method for quitting in Scandinavian countries,^{109–111} and previous observational studies using self-reported data confirmed that compared with the NRT, snus increased probability of cessation,¹¹² presumably owing to the nicotine uptake from snus that resembles that of combustible tobacco compared to latter approach.^{112–114} Nevertheless, the degree of evidence was low, suggesting further research is currently needed to expand the evidence base for the utility, as well as safety, of snus as a reduction/cessation aid.

Different forms and delivery methods of NRT had been evaluated by the included studies, including patches,^{90,92,95} inhaler,⁹² mouth sprays,⁸⁹ gum/lozenges,⁹⁵ or comparison of different forms.^{92,95} Combined NRT products had been consistently reported as superior to assist cessation up to 52 weeks^{95,115–117} and that NRT can increase the chance to successfully stop smoking.¹⁷ A previous review showed

that combination NRT produced greatest benefits relative to monotherapy for smoking cessation.¹¹⁸ It has been estimated that the use of different forms of NRT resulted in more adequate nicotine replacement from various mechanisms, possibly generating additive effects (ie, patch releases steady-state nicotine serum level to prevent acute withdrawal, while another NRT form, eg, gum/lozenge, may provide a coping mechanism addressing the behavioral urge of smoking).^{49,116,117} Our restriction to include references in the last 10 years might be limiting the effectiveness of NRT in smoking reduction/cessation because the availability of NRT products and their role had been assessed extensively since as early as the 1980s.¹⁷ However, the reason for our restriction was to showcase and focus on the most recent evidence on alternative tobacco and nicotine products.

As nicotine may interfere with the cardiovascular system, presumably through sympathetic neural stimulation and systemic catecholamine release, cardiovascular safety profile associated with NRT use has been extensively examined.^{23,89,91,93–95,119–121} Relatively long-term (five-year observation period) impact of NRT gum use was assessed by Murray et al, which showed that long-term exposure of this intervention was not associated with major adverse cardiovascular events.¹¹⁹ Among patients with a history of acute coronary syndrome, no excess risk of recurrent cardiovascular events was observed following the use of NRT in this high-risk population.¹²¹ As NRT delivers nicotine without a combustion process, the risk might be lower compared to that of EC,²³ nevertheless, current evidence remains unclear with regard to this comparison, and further robust investigation is required.

Alternative tobacco and nicotine products, including EC, smokeless tobacco, and NRT, are a current development in tobacco harm reduction.^{23,122} According to evidence gathered by this review as well as previous research,^{17,23,34,36,38,40} these approaches can be considered to be less harmful in a means of causing fewer adverse events compared to a cigarette and has the potential to assist smoking reduction and even cessation. Among smokers, the urge to smoke is often tough to break, and relapse is prevalent even for those who intend to quit smoking.⁵⁶ Therefore, to prevent tobacco-related morbidity and mortality, there is an urgency for alternative and more efficient means to reduce the harms caused by a particular behaviour. The approach in tobacco harm reduction includes amending and adjusting regulations that potentially can escalate damages, empowering people and policymakers

with accurate information and evidence-based policy, and suggesting alternatives and substitutions of lower-risk products that may further promote the cessation of cigarette smoking to current smokers.¹²³ In addition, to ensure efficient resource allocation for such policy, more economic evaluation studies comparing clinical effectiveness and cost of different alternative tobacco and nicotine products would be valuable to support evidence-based public health initiatives.⁹⁶

Furthermore, the strength of our review lies in the provision of comprehensive information on the role of different types of alternative tobacco and nicotine products in smoking reduction/cessation, as well as their potential safety issues. In addition, we used extensive search strategies, resulting in a relatively large number of included studies. Nevertheless, this review also has limitations. First, due to heterogeneity of the included studies, we were unable to conduct a meta-analysis, nevertheless a narrative review has been provided outlining current evidence on this topic and highlighting gap that remains unexplored for future studies. Another limitation was the risk of publication bias since we did not search grey literature, as we only included peer-reviewed published studies to ensure comparable study quality.

Conclusion

The results suggest that the use of alternative tobacco and nicotine products has been shown to potentially influence smoking reduction and cessation process, with various degree of effectiveness between different products. Available evidence indicated that these products are generally well-tolerated following short to medium-term use. The most common adverse events reported included mouth and throat-related irritation, dry cough, headache, and changes in pulmonary laboratory functions which were considerably milder than with conventional cigarettes. These findings are also highlighting the potential role of these products in a tobacco harm reduction approach. Further studies should focus on investigating long-term outcome, safety and effectiveness of alternative tobacco and nicotine products and also on monitoring both product use and awareness to better inform smoking reduction/cessation policy.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and [Table S1](#).

Author Contributions

Study conception and design: NZ, FVP, WNI, AAS; search strategy: NZ, FVP, AAS; study screening: NZ, FVP, WNI, AAS; data organization and presentation: NZ, FVP, RA, MIB, IMP; appraisal of included studies: NZ, FVP, WNI; data analysis and interpretation: NZ, FVP, WNI, RA, AAS; initial manuscript drafting: NZ, WNI; manuscript review and finalization: NZ, FVP, WNI, RA, IMP, MIB, RL, AA, AAS. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

This research was funded by the Center of Excellence in Higher Education for Pharmaceutical Care Innovation, Universitas Padjadjaran.

Disclosure

The authors reported no conflicts of interest in this work.

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