

Systematic reviews and meta-analyses of electronic cigarettes for smoking cessation published since 2020

Peer-reviewed publications

2023

Banks E AM, Yazidjoglou A, Brown S, Nguyen M, Martin M, Beckwith K, Daluwatta A, Campbell S, Joshy G. Electronic cigarettes and health outcomes: umbrella and systematic review of the global evidence. *Med J Aust.* 2023 Mar 20. doi: 10.5694/mja2.51890. Epub ahead of print. PMID: 36939271.

- 11 RCTs published and reviews published to November 2022
- **Results/conclusions:**
 - Use of freebase nicotine e-cigarettes with clinical support is more efficacious for assisting smoking cessation than nicotine replacement therapy, or than no intervention or usual care: limited evidence. Trials in which efficacy was found used products with freebase nicotine concentrations of no more than 20 mg/mL.
 - Efficacy of nicotine e-cigarettes for smoking cessation, compared with non-nicotine e-cigarettes: insufficient evidence.
 - Efficacy of non-nicotine e-cigarettes for smoking cessation, compared with counselling or nicotine replacement therapy: insufficient evidence.
 - Efficacy of non-clinical use of freebase nicotine e-cigarettes for assisting smoking cessation: insufficient evidence.
 - Efficacy of nicotine salt products for assisting smoking cessation: no available evidence.
 - Use of nicotine e-cigarettes for assisting smoking cessation results in greater exposure to nicotine (smoking, exclusive e-cigarette use or dual smoking/e-cigarette use) than nicotine replacement therapy: limited evidence.

2022:

Hanewinkel R, Niederberger K, Pedersen A, Unger JB, Galimov A. E-cigarettes and nicotine abstinence: a meta-analysis of randomised controlled trials. *Eur Respir Rev.* 2022 Mar 23;31(163):210215.

- RCTs comparing e-cigarettes and NRT to July 2021
- 4 studies representing 1598 adult participants. (Bonevski 2021, Bulet 2013, Hajek, 2019, Lee, 2018)
- **Results/Conclusion:** Among successful cigarette quitters, the risk of allocated product use by the end of the observational time was higher for e-cigarette users compared to NRT (risk ratio 8.94 (95% CI 3.98-20.07)). E-cigarette users had higher cigarette smoking cessation rates compared to NRT users (risk ratio 1.58 (95% CI 1.20-2.08)). The use of e-cigarettes as a therapeutic intervention for smoking cessation may lead to permanent nicotine dependence.

Hartmann-Boyce J, Lindson N, Butler AR, McRobbie H, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Fanshawe TR, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev.* 2022 Nov 17;11(11):

- RCTs published to July 2022
- 6 studies included with 2378 participants to assess e-cigarettes vs. NRT. (Bullen 2013, Hajek 2019, Lee 2018, Myers-Smith 2022, Russell 2021, Russell 2021.)

- **Results/Conclusions:** Nicotine e-cigarettes can help people to stop smoking for at least six months. Evidence shows they work better than nicotine replacement therapy. “high certainty”

Li J, Hui X, Fu J, Ahmed MM, Yao L, Yang K. Electronic cigarettes versus nicotine-replacement therapy for smoking cessation: A systematic review and meta-analysis of randomized controlled trials. *Tob Induc Dis.* 2022 Oct 20;20:90.

- RCTs published to October 2021
- 5 studies included with 1748 participants (Bonevski 2021, Bullen 2014, Hajek 2019, Lee 2018, Lee 2019)
- **Results/Conclusions:** E-cigarettes appeared to be superior to NRT in ≥ 6 months continuous abstinence rate and 7-day point abstinence rate. At short-term duration, we found no evidence that e-cigarettes compared to NRT increased the < 6 months continuous abstinence rate and 7-day point abstinence rate.

Vanderkam P, Bonneau A, Kinouani S, Dzeraviashka P, Castera P, Besnier M, Binder P, Doux N, Jaafari N, Lafay-Chebassier C. Duration of the effectiveness of nicotine electronic cigarettes on smoking cessation and reduction: Systematic review and meta-analysis. *Front Psychiatry.* 2022 Aug 4;13:915946.

- RCT of daily adult smokers published to March 23, 2022
- 7 studies included (Bullen 2013, Caponnetto, 2013, Cobb 2021, Eisenberg 2020, Hajek 2019, Lee 2020, Lucchiari 2020)
- **Results/Conclusions:** With regard to smoking reduction, the electronic cigarette with nicotine is significantly more effective than NRT at the end of the intervention and follow-up periods [respectively RR: 1.48 (CI 95%: 1.04-2.10) and RR: 1.47 (CI 95%: 1.18-1.82)] and non-nicotine electronic cigarette in the long term [RR: 1.31 (CI 95%: 1.02-1.68)]. This meta-analysis shows the duration of the effectiveness of the nicotine electronic cigarette vs. non-nicotine electronic cigarette and NRT on smoking cessation and reduction. There are still uncertainties about the risks of its long-term use and its potential role as a gateway into smoking, particularly among young people.

2021:

Chan GCK, Stjepanović D, Lim C, Sun T, Shanmuga Anandan A, Connor JP, Gartner C, Hall WD, Leung J. A systematic review of randomized controlled trials and network meta-analysis of e-cigarettes for smoking cessation. *Addict Behav.* 2021 Aug;119:106912. (not open access)

- RCT's comparing e-cigarettes to NRT.
- 7 trials included (seemingly Lee 2019, Caponnetto 2013, Halpern 2018, Hajek 2019, Bullen 2013, Walker 2020, Scherpof 2014)
- **Conclusion:** Smokers assigned to use nicotine e-cigarettes were more likely to remain abstinent from smoking than those assigned to use licensed NRT, and both were more effective than usual care or placebo conditions. More high quality studies are required to ascertain the effect of e-cigarette on smoking cessation due to risk of bias in the included studies.

Grabovac I, Oberndorfer M, Fischer J, Wiesinger W, Haider S, Dorner TE. Effectiveness of Electronic Cigarettes in Smoking Cessation: A Systematic Review and Meta-analysis. *Nicotine Tob Res.* 2021 Mar 19;23(4):625-634.

- RCTs comparing electronic cigarettes with established smoking cessation interventions published to June 2020.
- 12 studies for systematic review and 9 studies for meta analysis.
- **Results/Conclusion:** Our results suggest that nicotine ECs may be more effective in smoking cessation when compared with placebo ECs or NRT. When compared with counseling alone, nicotine ECs are more effective short term, but its effectiveness appears to diminish with later follow-ups. Given the small

number of studies, heterogeneous design, and the overall moderate to low quality of evidence, it is not possible to offer clear recommendations.

Hedman L, Galanti MR, Ryk L, Gilljam H, Adermark L. Electronic cigarette use and smoking cessation in cohort studies and randomized trials: A systematic review and meta-analysis. *Tob Prev Cessat.* 2021 Oct 13;7:62.

- Longitudinal design or RCT published between January 1 1990 to November 2019
- 28 cohort studies and 8 papers from 7 RCTs (Bullen 2013, Carpenter 2017, Hajek 2019, Holliday 2019, Lee 2018, Masiero 2019, Walker 2019).
- **Results/Conclusions:** We did not find quality evidence for an association between e-cigarette use and smoking cessation. Although RCTs tended to support a more positive association between e-cigarette use and smoking cessation than the cohort studies, the grading of evidence was consistently low.

Ibrahim S, Habiballah M, Sayed IE. Efficacy of Electronic Cigarettes for Smoking Cessation: A Systematic Review and Meta-Analysis. *Am J Health Promot.* 2021 Mar;35(3):442-455.

- RCT to December 2019
- 12 trials involving 9,863 participants. (Walker 2019, Lee 2018, Caponnetto 2013, Lee 2018, Hajek 2019, Tseng 2016, Bullen 2013, Baldassarri 2018, Halpern 2018, Carpenter 2017, Adriaens 2014, Bianco 2019)
- **Results/Conclusion** Very low certainty evidence supported e-cigarettes to help quit smoking in the short term. There is not enough evidence to determine if e-cigarettes are a safe and efficacious means of smoking cessation in the long term (12+ months).

Pound CM, Zhang JZ, Kodua AT, Sampson M. Smoking cessation in individuals who use vaping as compared with traditional nicotine replacement therapies: a systematic review and meta-analysis. *BMJ Open.* 2021 Feb 22;11(2):e044222.

- RCT's in which ENDS were compared with NRT in smokers published to June 2020.
- 6 RCTs included (Bullen 2013, Eisenhofer 2015, Hajek 2019, Hatsukami 2019, Lee 2019, Lee 2018).
- **Results/Conclusion:** We found no difference in smoking cessation, harms and smoking reduction between e-cigarette and NRT users. However, the quality of the evidence was low. Further research is needed before widespread recommendations are made with regard to the use of ENDS.

Quigley JM, Walsh C, Lee C, Long J, Kennelly H, McCarthy A, Kavanagh P. Efficacy and safety of electronic cigarettes as a smoking cessation intervention: A systematic review and network meta-analysis. *Tob Prev Cessat.* 2021 Nov 22;7:69.

- RCTs comparing e-cigarettes and NRT published to May 2021
- 10 studies included (Bullen 2013, Caponnetto 2013, Hajek 2019, Halpern 2018, Lee 2019, Masiero 2019, Holliday 2019, Hatsukami 2020, Lee 2018, Eisenberg 2020).
- **Results/Conclusions:** This systematic review and NMA indicates that there is no clear evidence of a difference in effect between nicotine containing e-cigarettes and NRT on incidences of smoking cessation at 24–26 weeks, and substantial uncertainty remains.

Thomas KH, Dalili MN, López-López JA, Keeney E, Phillippo DM, Munafò MR, Stevenson M, Caldwell DM, Welton NJ. Comparative clinical effectiveness and safety of tobacco cessation pharmacotherapies and electronic cigarettes: a systematic review and network meta-analysis of randomized controlled trials. *Addiction.* 2022 Apr;117(4):861-876.

- RCTs in adult smokers and smokeless tobacco users published before February 2019.
- 363 studies

- **Results/Conclusions:** Most tobacco cessation monotherapies and combination therapies are more effective than placebo at helping participants to achieve sustained abstinence, with varenicline appearing to be most effective based on current evidence. / Although e-cigarettes showed promise as cessation tools, more research is needed on their long-term effectiveness and safety, preferably in studies with active interventions as comparators

Zakiyah N, Purwadi FV, Insani WN, Abdulah R, Puspitasari IM, Barliana MI, Lesmana R, Amaliya A, Suwantika AA. Effectiveness and Safety Profile of Alternative Tobacco and Nicotine Products for Smoking Reduction and Cessation: A Systematic Review. *J Multidiscip Healthc.* 2021 Jul 23;14:1955-1975. doi: 10.2147/JMDH.S319727. PMID: 34326646; PMCID: PMC8315778

- Studies indexed before December 2020.
- 7 RCTs (Hajek, 2019, Bullen, 2013, Caponnetto, 2013, Adriaens 2014, Cibella, 2016, Walker 2020, Baldassarri, 2018) and cohort studies
- **Conclusions:** 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.

Zhang YY, Bu FL, Dong F, Wang JH, Zhu SJ, Zhang XW, Robinson N, Liu JP. The effect of e-cigarettes on smoking cessation and cigarette smoking initiation: An evidence-based rapid review and meta-analysis. *Tob Induc Dis.* 2021 Jan 13;19:04.

- RCTs and Cohort studies published between 2015 and 2020.
- 6 Systematic Reviews, 5 RCTS (Hajek 2019, Lee 2019, Li 2019, Tseng 2016, Halpern 2018), and 24 cohort studies.
- **Results/Conclusion:** We found no difference in smoking cessation, harms and smoking reduction between e-cigarette and NRT users. However, the quality of the evidence was low. Further research is needed before widespread recommendations are made with regard to the use of ENDS.
- Meta-analysis of 5 RCTs suggested that e-cigarettes were superior to NRT or placebo for smoking cessation. Evidence from 9 cohort studies showed that e-cigarette use was not associated with cessation. In terms of smoking initiation, adolescents who ever used e-cigarettes had a greater risk for smoking initiation than non-users.

2020:

Liu X, Lu W, Liao S, Deng Z, Zhang Z, Liu Y, Lu W. Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article). *Medicine (Baltimore).* 2018 May;97(19):e0324.

- Studies written in English or Chinese until July 2017.
- 3 RCTs (Caponnetto 2018, Bullen 2013, Bullen 2010), 7 observational studies and 4 online surveys
- **Results/Conclusion** Our findings suggest that e-cigarettes are moderately effective with regard to smoking reduction and smoking cessation. CO levels are unreliable for evaluating the efficacy of e-cigarettes. E-cigarette related adverse events frequently occur, especially due to high-dose nicotine-containing cartridges.

Wang RJ, Bhadriraju S, Glantz SA. E-Cigarette Use and Adult Cigarette Smoking Cessation: A Meta-Analysis. *Am J Public Health.* 2021 Feb;111(2):230-246.

- RCTs and observational studies published to January 2020.
- 9 RCTs (Bullen 2013, Hajek 2019, Halpern 2018, Hatsukami 2018, Holliday 2019, Lee 2018, Lee 2018, Lucchiari 2020, Walker 2020) , 41 cohort studies, 14 cross-sectional studies.

- **Results/Conclusion:** E-cigarette use as a consumer product is not significantly associated with cigarette smoking cessation in the general adult population. E-cigarettes may warrant consideration as a prescription drug to be used as part of a clinically supervised smoking cessation intervention, provided that the associated risks are commensurate with the benefit.

Other reports

Banks E, Yazidjoglou A, Brown S, Day C. Nicotine e-cigarettes for smoking cessation: Evidence to support guideline development. Report prepared for the Royal Australian College of General Practitioners, September 2021
<https://www.racgp.org.au/FSDEDEV/media/documents/Clinical%20Resources/Appendix-Evidence-to-Decision-Report.pdf>.

Banks E, Yazidjoglou A, Brown S, Nguyen M, Martin M, Beckwith K, Daluwatta A, Campbell S, Joshy G. Electronic cigarettes and health outcomes: systematic review of global evidence Report for the Australian Department of Health. National Centre for Epidemiology and Population
https://www.nhmrc.gov.au/sites/default/files/documents/attachments/ecigarettes/Electronic_cigarettes_and_health_outcomes_%20systematic_review_of_evidence.pdf

- Reviewed 9 RCT's (Carpenter 2017, Halpern 2018, Lucciani 2019, Bullen 2013, Capponetto 2013, Bullen 2013, Hajek 2019, Lee 2019).
- **Results/Conclusion** For people who have tried to achieve smoking cessation with TGA-approved pharmacotherapies combined with behavioural intervention but failed and are still motivated to quit smoking, e-cigarettes may be a reasonable intervention to recommend. However, this needs to be preceded by an evidence-informed shared-decision making process, whereby the patient is aware of the following caveats: 1. Due to the lack of available evidence, the long-term health effects of e-cigarettes are unknown. 2. E-cigarettes are not registered therapeutic goods in Australia and therefore their safety, efficacy and quality have not been established. 3. There is a lack of uniformity in delivery devices and e-liquid constituents which increases the uncertainties associated with their use. 4. TGO 110 permits extremely high concentrations of liquid nicotine to be prescribed and dispensed so, if prescribed, the patient must fully understand the potential consequences of high concentration liquid nicotine and take steps to minimise risk. 5. In order to maximise possible benefit and minimise risk of harms, dual use should be avoided and long-term use should be minimised.

Scientific Committee on Health, Environmental and Emerging Risks SCHEER. Opinion on electronic cigarettes. European Commission, 2021.

- Did not conduct a meta-analysis, but reviewed RCT. Did not consider cohort studies.
- **Conclusion:** Regarding the role of electronic cigarettes in cessation of traditional tobacco smoking, the SCHEER concludes that there is weak evidence for the support of electronic cigarettes' effectiveness in helping smokers to quit while the evidence on smoking reduction is assessed as weak to moderate.

Haut Conseil de la santé publique. France. Avis relatif aux bénéfices-risques de la cigarette électronique. 2021

- Did not conduct a meta-analysis, but reviewed RCT. Did not consider cohort studies.
- **Conclusion:** There is a strong assumption that electronic nicotine delivery systems (ENDS) could become first-line nicotine replacement therapies, but the number of trials is small and their methodological quality is below that recommended for such therapeutic trials...None of the studies reported here uses rigorous methodology such as that required for therapeutic trials in other therapeutic areas or for registration of health products in a therapeutic indication. This methodological deficiency results in uncertainty about the benefit/risk ratio of ENDS. For this reason, international guidelines do not

recommend ENDS with or without nicotine as a therapeutic tool in the management of smoking cessation by health professionals.

United States Public Health Service Office of the Surgeon General; National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. Smoking Cessation: A Report of the Surgeon General [Internet]. Washington (DC): US Department of Health and Human Services; 2020. PMID: 32255575

- Did not conduct a meta-analysis, but reviewed published reports on RCT, observational studies, metaanalyses and systematic reviews. The absence of RCT's conducted in the USA was noted.
- **Conclusion:** E-cigarettes, a continually changing and heterogeneous group of products, are used in a variety of ways. Consequently, it is difficult to make generalizations about efficacy for cessation based on clinical trials involving a particular e-cigarette, and there is presently inadequate evidence to conclude that e-cigarettes, in general, increase smoking cessation.

US Preventive Services Task Force. Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Persons: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325(3):265–279. doi:10.1001/jama.2020.25019 / Patnode CD, Henderson JT, Coppola EL, Melnikow J, Durbin S, Thomas RG.

Interventions for Tobacco Cessation in Adults, Including Pregnant Persons: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2021;325(3):280–298.

- Considered 67 reviews addressing pharmacotherapy and 9 trials for e-cigarettes. (Bullen 2013, Caponnetto 2013, Hajek 2019, Lee 2019, Walker 2019, Carpenter 2017, Cravo 2016, Masiero 2017, Tseng 2016).
- **Conclusion:** There is strong evidence that a range of pharmacologic and behavioral interventions, both individually and in combination, are effective in increasing smoking cessation in nonpregnant adults. In pregnancy, behavioral interventions are effective for smoking cessation, but data are limited on the use of pharmacotherapy for smoking cessation. Data on the effectiveness and safety of electronic cigarettes for smoking cessation among adults are also limited and results are inconsistent. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant persons. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of e-cigarettes for tobacco cessation in adults, including pregnant persons. The USPSTF recommends that clinicians direct patients who use tobacco to other tobacco cessation interventions with proven effectiveness and established safety.