EXECUTIVE SUMMARY

The Lower-Risk Nicotine Use Guidelines (LRNUG) present the current state of evidence on tobacco/nicotine products, highlighting modifiable behaviours that can help reduce the negative health outcomes associated with tobacco/nicotine product use. They have been designed to guide people who use, or are thinking about using nicotine, on how to lower the risk associated with various nicotine products. The products covered in the Guidelines include heated tobacco products, smokeless tobacco (chew and snus), waterpipes, and e-cigarettes/vapes.

METHODOLOGY: Search strategy and execution were developed by the Centre for Addiction and Mental Health and the Centre for Effective Practice. A comprehensive literature search for systematic reviews published between January 2014 and October 2019 was performed in MEDLINE, PsycInfo, Cochrane Database of Systematic Reviews, and Embase, with a focus on nicotine products (e-cigarettes, waterpipe, smokeless tobacco, heat-not-burn) and selected health outcomes (cancer, CVD and stroke, respiratory health, addiction, cessation, reproductive health). A supplemental search to identify additional Clinical Practice Guidelines (CPGs) published from 2014 to 2019 was also performed.

Quality assessment employed the AGREE II (Appraisal of Guidelines for Research and Evaluation) instrument for CPGs, and the AMSTAR instrument for systematic reviews. Due to the limited nature of e-cigarette study methodology, the use of the full AMSTAR instrument would have resulted in a prohibitively small pool of systematic reviews. Therefore, a rapid AMSTAR, using 2 key metrics (comprehensive literature search and assessment of scientific quality of included studies), was used to enable the inclusion of many well-done studies that nonetheless would not pass the high bar of the full AMSTAR criteria, while excluding less rigorously performed reviews. The full list of references included in Guideline development is available below in Table 1.

GUIDELINE DEVELOPMENT MEETING: The Guideline Development Group (GDG) consisted of nicotine experts from across Canada, chosen for their expertise in the field and diversity of perspectives (see below for full list of GDG members). All members of the GDG submitted GIN-inspired Conflicts of Interest declarations at two separate time points throughout the process.

On November 18-9, 2019, the GDG convened for an in-person meeting in which fourteen voting members gathered to assess the quality of the literature; draft evidence-based recommendations on the use of the different products; and vote to confirm the final language to be used in the recommendations. Using a facilitated consensus-building approach, the group drafted and finalized ten evidence-based recommendations, supported by group consensus on the quality of the evidence base and the strength of each recommendation. Summary statements and additional considerations were drafted at this meeting and confirmed post-gathering via electronic communication.

Feedback from the GDG highlighted the fact that limiting the inclusion criteria to only systematic reviews resulted in an evidence gap for new e-cigarette literature. To address this gap, an updated literature search was conducted targeting high-quality RCTs on e-cigarettes published between 2015-2020. Quality of included RCTs was assessed using the Cochrane Risk of Bias Tool 2.0 (RoB tool) (Sterne et al 2019).

Results from this supplemental search were mapped to determine support of, or opposition to, the recommendations developed by the GDG. A secondary 'up-to-the-moment' search was conducted in January 2021 to ensure that the recommendations were supported by available literature up to that date. A secure, anonymous electronic voting tool was used in March 2021 by the GDG to vote on necessary changes to the recommendations, including level of evidence and strength of the recommendation.

GUIDELINE DEVELOPMENT GROUP (GDG) MEMBERS:

The following list details the Guideline Development Group members' credentials, affiliations, and reported conflicts of interest within the past 5 years:

Peter Selby, MBBS, CCFP(AM), FCFP, MHSc, dipABAM, DFASAM

Centre for Addiction and Mental Health; University of Toronto

Dr. Selby reports receipt of consulting fees from Johnson & Johnson, NVision Insight Group and Myelin and Associates; grant/research support from Pfizer, Bhasin Consulting Fund Inc., Canadian Institutes of Health Research, Health Canada, Canadian Cancer Society, Medical Psychiatry Alliance, Ontario Ministry of Health and Long-Term Care, Canadian Partnership Against Cancer, and the Public Health Agency of Canada; and has been a subject matter expert or chair on advisory boards for Pfizer Canada Inc, and Johnson & Johnson. Through an open tender process, Dr. Selby reports that Johnson & Johnson, Novartis and Pfizer Inc. are vendors of record for having provided free/discounted smoking cessation pharmacotherapy.

John Atkinson, MSW, BA, ONi

Canadian Cancer Society

Mr. Atkinson has no conflicts of interest to report.

Bruce Baskerville, MHA, PhD, CE

Canadian Institutes of Health Research

Dr. Baskerville reports receiving grant/research support from the Canadian Institutes of Health Research and Public Health Agency of Canada for research on tobacco and vaping cessation.

Mark Eisenberg, MD, IMHL, MPH

Jewish General Hospital; McGill University

Dr. Eisenberg reports pending and receiving grants/research support from Canadian Institutes of Health Research.

Brent Friesen, MD, FRCPC

Alberta Health Services

Dr. Friesen reports employment from Alberta Health Services Tobacco Reduction Program; consulting fees as the Acting Chief Medical Officer of Health for Alberta Health; expert testimony for the Alberta government for noncompliance with laws regarding tobacco; grants/research support from Alberta Cancer Prevention Legacy Fund; and acts as a surveyor with Accreditation Canada and Accreditation Canada International.

Milan Khara, MBChB, CCFP, Dip. ABAM

Vancouver Coastal Health; University of British Columbia

Dr. Khara has no conflicts of interest to report.

Jane Ling, R.Ph., BScPhm

North Durham Family Health Team; Pharmacists for a Smoke Free Canada

Ms. Ling reports receipt of honoraria from Johnson & Johnson and Pfizer.

Claudia Mariano, MSc, NP

Nurse Practitioners Association of Ontario

Ms. Mariano has no conflicts of interest to report.

Nadia Minian, PhD, MA

CAMH

Dr. Minian has no conflicts of interest to report.

Alice Ordean, MD

St. Joseph's Health Centre; University of Toronto

Dr. Ordean has no conflicts of interest to report.

Ron Pohar, BSc.Pharm, APA

Consultant Pharmacist

Mr. Pohar has no conflicts of interest to report.

Robert Reid, PhD, MBA

University of Ottawa Heart Institute

Dr. Reid reports receiving honoraria from Pfizer Inc. and Johnson & Johnson for speaking engagements; stock ownership of Johnson & Johnson; and grant/research support received from Pfizer for clinical trial.

Robert Schwartz, PhD

Ontario Tobacco Research Unit; University of Toronto

Dr. Schwartz reports receiving grant/research support from the Canadian Institutes of Health Research, Health Canada, and the National Institutes of Health

Laurie Zawertailo, PhD

CAMH; University of Toronto

Dr. Zawertailo has no conflicts of interest to report.

E-cigarettes	Article Type
Boulay M-È, Henry C, Bossé Y, Boulet L-P, Morissette MC. Acute effects of nicotine-free and flavour-free electronic cigarette use on lung functions in healthy and asthmatic individuals. Respir Res. 2017; 10;18(1):33.	Randomized Control Trial (RCT)
Callahan-Lyon, P. Electronic cigarettes: human health effects. Tob Control. 2014; 23 Suppl 2: ii36-40.	Systematic Review (SR
Campagna D, Cibella F, Caponnetto P, Amaradio MD, Caruso M, Morjaria JB, et al. Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes. Eur J Clin Invest. 2016; 46(8):698–706.	RCT
Cardenas VM, Fishbach LA, Chowdhury P. The use of electronic nicotine delivery systems during pregnancy and the reproductive outcomes: A systematic review of the literature. Tob Induc Dis. 2019; 17:52.	SR
Chatterjee K, Alzghoul B, Innabi A, Meena N. Is vaping a gateway to smoking: a review of the longitudinal studies. Int J Adolesc Med Health. 2016; 30(3).	Review (R)
Chaumont M, Bernard A, Pochet S, Mélot C, El Khattabi C, Reye F, et al. High-Wattage E-Cigarettes Induce Tissue Hypoxia and Lower Airway Injury: A Randomized Clinical Trial. Am J Respir Crit Care Med. 2018; 198(1):123–126.	RCT
Chaumont M, de Becker B, Zaher W, Culie A, Deprez G, Melot C, et al. Differential Effects of E-Cigarette on Microvascular Endothelial Function, Arterial Stiffness and Oxidative Stress: A Randomized Crossover Trial. Sci rep. 2018; 8(1):10378.	RCT
Chaumont M, Tagliatti V, Channan EM, Colet J-M, Bernard A, Morra S, et al. Short halt in vaping modifies cardiorespiratory parameters and urine metabolome: a randomized trial. Am J Physiol Lung Cell Mol Physiol. 2020; 318(2):L331–344.	RCT
Chaumont M, van de Borne P, Bernard A, Van Muylem A, Deprez G, Ullmo J, et al. Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchange disturbances: results from two randomized clinical trials. Am J Physiol Lung Cell Mol Physiol. 2019; 316(5):L705–19.	RCT
Cibella F, Campagna D, Caponnetto P, Amaradio MD, Caruso M, Russo C, et al. Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. Clin Sci. 2016; 130(21):1929–1937.	RCT
Copp SR, Collins JL, Dar R, Barrett SP. The effects of nicotine stimulus and response expectancies on male and female smokers' responses to nicotine-free electronic cigarettes. Addictive Behaviors. 2015; 40:144–147.	RCT
Czoli CD, Fong GT, Goniewicz ML, Hammond D. Biomarkers of Exposure Among "Dual Users" of Tobacco Cigarettes and Electronic Cigarettes in Canada. Nicotine Tob Res. 2019; 21(9):1259–1266.	RCT
De La Garza R, Shuman SL, Yammine L, Yoon JH, Salas R, Holst M. A Pilot Study of E-Cigarette Naïve Cigarette Smokers and the Effects on Craving After Acute Exposure to E-Cigarettes in the Laboratory. Am J Addict. 2019; 28(5):361–366.	RCT
D'Ruiz CD, Graff DW, Yan XS. Nicotine delivery, tolerability and reduction of smoking urge in smokers following short-term use of one brand of electronic cigarettes. BMC Public Health. 2015; 15:991.	RCT
De La Garza R, Shuman SL, Yammine L, Yoon JH, Salas R, Holst M. A Pilot Study of E-Cigarette Naïve Cigarette Smokers and the Effects on Craving After Acute Exposure to E-Cigarettes in the Laboratory. Am J Addict. 2019; 28(5):361–366.	RCT
D'Ruiz CD, Graff DW, Robinson E. Reductions in biomarkers of exposure, impacts on smoking urge and assessment of product use and tolerability in adult smokers following partial or complete substitution of cigarettes with electronic cigarettes. BMC Public Health. 2016; 16:543.	RCT
Eisenberg MJ, Hébert-Losier A, Windle SB, Greenspoon T, Brandys T, Fülöp T, et al. Effect of e-Cigarettes Plus Counseling vs Counseling Alone on Smoking Cessation: A Randomized Clinical Trial. JAMA. 2020; 324(18):1844–1854.	RCT
Fearon IM, Eldridge A, Gale N, Shepperd CJ, McEwan M, Camacho OM, et al. E-cigarette Nicotine Delivery: Data and Learnings from Pharmacokinetic Studies. American Journal of Health Behavior. 2017; 41(1):16–32.	RCT
Ferrari M, Zanasi A, Nardi E, Morselli Labate AM, Ceriana P, Balestrino A, et al. Short-term effects of a nicotine-free e-cigarette compared to a traditional cigarette in smokers and non-smokers. BMC Pulm Med. 2015; 15:120.	RCT
El Dib R, Suzumura EA, Akl EA, Gomaa H, Agarwal A, et al. Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis. BMJ Open. 2017; 7(2):e012680.	Systematic Review and Meta-analysis (SR & MA)
Flach S, Maniam P, Manickavasagam J. E-cigarettes and head and neck cancers: A systematic review of the current literature. Clin Otolaryngol. 2019; 44(5):749-756.	SR

Gualano MR, Passi S, Bert F, La Torre G, Scaioli G, Siliquini R. Electronic cigarettes: assessing the efficacy and the adverse effects through a systematic review of published studies. J Public Health (Oxf). 2015; 37(3):488-497.	SR
Hajek P, Etter JF, Benowitz N, Eissenberg T, McRobbie H. Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. Addiction. 2014; 109(11):1801-1810.	R
Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead L, Hajek P. (2016). Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2016; 9:CD010216.	SR
Hatsukami DK, Meier E, Lindgren BR, Anderson A, Reisinger SA, Norton KJ, et al. A Randomized Clinical Trial Examining the Effects of Instructions for Electronic Cigarette Use on Smoking-Related Behaviors and Biomarkers of Exposure. Nicotine Tob Res. 2020; 22(9):1524–1532.	RCT
lay J, Pfaunmiller EL, Huang NJ, Cohen G, Graff DW. Five-Day Changes in Biomarkers of Exposure Among Adult Smokers After Completely Switching From Combustible Cigarettes to a Nicotine-Salt Pod System. Nicotine Tob Res. 2020; 22(8):1285–1293.	RCT
Calkhoran S and Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and neta-analysis. Lancet Respir Med. 2016; 4(2):116-128.	SR & MA
Kennedy CD, van Schalkwyk MC, McKee M, Pisinger C. The cardiovascular effects of electronic cigarettes: A systematic review of experimental studies. Prev Med. 2019; 127:105770.	SR
Choudigian S, Devji T, Lytvyn L, Campbell K, Hopkins R, O'Reilly D. The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: a systematic review and a meta-analysis. Int J Public Health. 2016; 61(2):257-267.	SR & MA
iu, 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; 97(19):e0324.	SR & MA
Maglia M, Caponnetto P, Di Piazza J, La Torre D, Polosa R. Dual use of electronic cigarettes and classic cigarettes: a systematic eview. Addiction Research & Theory. 2018; 26(4):330-338.	SR
Malas M, van der Tempel J, Schwartz R, Minichiello A, Lightfoot C, et al. Electronic Cigarettes for Smoking Cessation: A Systematic Review. Nicotine Tob Res. 2016; 18(10):1926-1936.	SR
Masiero M, Lucchiari C, Mazzocco K, Veronesi G, Maisonneuve P, Jemos C, et al. E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled Trial. Nicotine Tob Res. 2019; 21(1):119–126.	RCT
McNeill A, Brose LS, Calder R, Bauld L, Robson D. Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England. 2018; London: Public Health England.	R
McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. Cochrane Database Syst Rev. 2014; 12:CD010216.	SR & MA
National Academies of Sciences, Engineering, and Medicine 2018. Public Health Consequences of E-Cigarettes: Consensus Study Report. Washington, DC: The National Academies Press. https://doi.org/10.17226/24952.	Clinical Practice Guideline (CPG)
D'Connell G, Graff DW, D'Ruiz CD. Reductions in biomarkers of exposure (BoE) to harmful or potentially harmful constituents HPHCs) following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. Toxicol Mech Methods. 2016; 26(6):443–454.	RCT
D'Connell G, Pritchard JD, Prue C, Thompson J, Verron T, Graff D, et al. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. Intern Emerg Med. 2019; 14(6):853–861.	RCT
Palmer AM, Brandon TH. How do electronic cigarettes affect cravings to smoke or vape? Parsing the influences of nicotine and expectancies using the balanced-placebo design. J Consult Clin Psychol. 2018; 86(5):486–491.	RCT
Poulianiti K, Karatzaferi C, Flouris AD, Fatouros IG, Koutedakis Y, Jamurtas AZ. Antioxidant responses following active and bassive smoking of tobacco and electronic cigarettes. Toxicol Mech Methods. 2016; 26(6):455–461.	RCT
Pulvers K, Nollen NL, Rice M, Schmid CH, Qu K, Benowitz NL, et al. Effect of Pod e-Cigarettes vs Cigarettes on Carcinogen Exposure Among African American and Latinx Smokers: A Randomized Clinical Trial. JAMA Network Open. 2020; 3(11): e2026324–e2026324.	RCT
Rahman MA, Hann N, Wilson A, Mnatzaganian, Worrall-Carter L. E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. PLoS One. 2015; 10(3):e0122544.	SR & MA
Riley HE, Berry-Bibee E, England LJ, Jamieson DJ, Marchbanks PA, Curtis KM. Hormonal contraception among electronic cigarette users and cardiovascular risk: a systematic review. Contraception. 2016; 93(3):190-208.	SR
Round EK, Chen P, Taylor AK, Schmidt E. Biomarkers of Tobacco Exposure Decrease After Smokers Switch to an E-Cigarette or Nicotine Gum. Nicotine Tob Res. 2019; 21(9):1239–1247.	RCT

	1
Siu AL and USPST Force. Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2015; 163(8):622-634.	CPG
Soneji S, Barrington-Trimis JL, Wills T, Leventhal AM, Unger JB, Gibson LA, et al. Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. JAMA Pediatr. 2017; 171(8):788-797.	SR & MA
seng T-Y, Ostroff JS, Campo A, Gerard M, Kirchner T, Rotrosen J, et al. A Randomized Trial Comparing the Effect of Nicotine /ersus Placebo Electronic Cigarettes on Smoking Reduction Among Young Adult Smokers. Nicotine Tob Res. 2016; 8(10):1937–1943.	RCT
/alentine GW, Jatlow PI, Coffman M, Nadim H, Gueorguieva R, Sofuoglu M. The effects of alcohol-containing e-cigarettes on young adult smokers. Drug Alcohol Depend. 2016; 159:272–276.	RCT
Wang M, Wang JW, Cao SS, Wang HQ, Hu RY. Cigarette Smoking and Electronic Cigarettes Use: A Meta-Analysis. Int J Environ Res Public Health. 2016; 13(1).	SR & MA
Whittington JR, Simmons PM, Phillips AM, Gammill SK, Cen R, Magann EF, Cardenas VM. The Use of Electronic Cigarettes in Pregnancy: A Review of the Literature. Obstet Gynecol Surv. 2018; 73(9):544-549.	SR
ruki D, Takeshige Y, Nakaya K, Futamura Y. Assessment of the exposure to harmful and potentially harmful constituents in nealthy Japanese smokers using a novel tobacco vapor product compared with conventional cigarettes and smoking abstinence. Regul Toxicol Pharmacol. 2018; 96:127–134.	RCT
Zucchet A and Schmaltz G. Electronic cigarettes—A review of the physiological health effects. FACETS. 2017; 2(1):575-609.	R
Burkey MD, Feirman S, Wang H, Choudhury SR, Grocer S, Johnston FM. The association between smokeless tobacco use and pancreatic adenocarcinoma: a systematic review. Cancer Epidemiol. 2014; 38(6):647-653.	SR
Gupta B and Johnson NW. Systematic review and meta-analysis of association of smokeless tobacco and of betel quid vithout tobacco with incidence of oral cancer in South Asia and the Pacific. PLoS ONE. 2014; 9(11):e113385.	SR & MA
Gupta S, Gupta R, Sinha DN, Mehrotra R. Relationship between type of smokeless tobacco & risk of cancer: A systematic eview. Indian J Med Res. 2018; 148(1):56-76.	SR
Gupta R, Gupta S, Sharma S, Sinha DN, Mehrotra R. Risk of coronary heart disease among smokeless tobacco users: Results of systematic review and meta-analysis of global data. Nicotine & Tobacco Research. 2019; 21(1):25-31.	SR & MA
namdar AS, Croucher RE, Chokhandre MK, Mashyakhy MH, Marinho VC. Maternal Smokeless Tobacco Use in Pregnancy and Adverse Health Outcomes in Newborns: A Systematic Review. Nicotine Tob Res. 2015; 17(9):1058-1066.	SR
Sinha DN, Abdulkader RS, Gupta PC. Smokeless tobacco-associated cancers: A systematic review and meta-analysis of Indian studies. Int J Cancer. 2016; 138(6): 1368-1379.	SR & MA
Sinha DN, Suliankatchi RA, Gupta PC, Thamarangsi T, Agarwal N, et al. Global burden of all-cause and cause-specific mortality due to smokeless tobacco use: systematic review and meta-analysis. Tob Control. 2018; 27(1):35-42.	SR & MA
Vidyasagaran AL, Siddiqi K, Kanaan M. Use of smokeless tobacco and risk of cardiovascular disease: A systematic review and meta-analysis. Eur J Prev Cardiol. 2016; 23(18):1970-1981.	SR & MA
Heat-not-burn	
Jankowski M, Brozk GM, Lawson J, Skoczynski S, Majek P, Zejda JE. New ideas, old problems? Heated tobacco products - a systematic review. Int J Occup Med Environ Health. 2019; 32(5):595-634.	SR
Khan Z, Khan S, Christianson L, Rehman S, Ekwunife O, Samkange-Zeeb F. Smokeless Tobacco and Oral Potentially Malignant Disorders in South Asia: A Systematic Review and Meta-analysis. Nicotine Tob Res. 2017; 20(1):12-21.	SR & MA

commissioned by Public Health England. 2018; London: Public Health England.

2019; 28(5):582-594.

McNeill A, Brose LS, Calder R, Bauld L, Robson D. Evidence review of e-cigarettes and heated tobacco products 2018. A report

Simonavicius E, McNeill A, Shahab L, Brose LS. Heat-not-burn tobacco products: a systematic literature review. Tob Control.

R

SR

Reproductive Health		
Cardenas VM, Fischbach LA, Chowdhury P. The use of electronic nicotine delivery systems during pregnancy and the reproductive outcomes: A systematic review of the literature." Tob Induc Dis. 2019; 17:52	SR	
Inamdar AS, Croucher RE, Chokhandre MK, Mashyakhy MH, Marinho VC. Maternal Smokeless Tobacco Use in Pregnancy and Adverse Health Outcomes in Newborns: A Systematic Review. Nicotine Tob Res. 2015; 17(9):1058-1066.	SR	
National Academies of Sciences, Engineering, and Medicine 2018. Public Health Consequences of E-Cigarettes: Consensus Study Report. Washington, DC: The National Academies Press. https://doi.org/10.17226/24952.	CPG	
Riley HE, Berry-Bibee E, England LJ, Jamieson DJ, Marchbanks PA, Curtis KM. Hormonal contraception among electronic cigarette users and cardiovascular risk: a systematic review. Contraception. 2016; 93(3):190-208.	SR	
Siu AL and USPST Force. Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2015; 163(8):622-634.	CPG	
Waziry R, Jawad M, Ballout RA, Al Akel M, Akl A E. The effects of waterpipe tobacco smoking on health outcomes: an updated systematic review and meta-analysis. Int J Epidemiol. 2017; 46(1):32-43.	SR & MA	
Whittington JR, Simmons PM, Phillips AM, Gammill SK, Cen R, Magann EF, Cardenas VM. The Use of Electronic Cigarettes in Pregnancy: A Review of the Literature. Obstet Gynecol Surv. 2018; 73(9):544-549.	SR	