

Pharmaceutical Benefits Scheme

Post-market Review

Post-market Review of Medicines Used for Smoking Cessation

Report to PBAC

ToR 1: Comparison of prescribing restrictions and clinical guidelines

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Abbreviations

Abbreviation	Full Name / Wording
ACT	Acceptance and Commitment Therapy Australian Capital Territory
AGREE	Appraisal of Guidelines for Research and Evaluation
BNF	British National Formulary
BUP	Bupropion
CAN-ADAPTT	Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment
CBT	Cognitive Behavioural Therapy
CLO	Clonidine
CMI	Consumer Medicines Information
COPD	Chronic Obstructive Pulmonary Disease
CPD	Cigarettes Per Day
CVD	Cardiovascular Disease
CYT	Cytisine
eTG	Electronic Therapeutic Guidelines
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HCP	Healthcare Provider
MI	Motivational Interviewing
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
NOR	Nortriptyline
NRT	Nicotine Replacement Therapy
NSW	New South Wales
NZ	New Zealand
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PI	Product Information
QFNL	Quit For New Life
QLD	Queensland
RACGP	Royal Australian College of General Practitioners
RPBS	Repatriation Pharmaceutical Benefits Schedule
RQ	Research Question
TGA	Therapeutic Goods Administration
ToR	Term of Reference

UK	United Kingdom
US	United States
USPSTF	United States Preventive Services Task Force
VAR	Varenicline
VIC	Victoria
WA	Western Australia

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Section 1: ToR 1

Comparison of prescribing restrictions and clinical guidelines

Collate the current clinical guidelines for medicines for smoking cessation and compare these to the Therapeutic Goods Administration (TGA) and Pharmaceutical Benefits Scheme (PBS) restrictions for these medicines

1.1 Key findings for ToR 1

RQ 1: identify and compare relevant clinical guidelines including Australian, Health service and international guidelines

- Twelve national (Australian) and four international guidelines were identified.
- National guidelines included three country-level guidelines from the Royal Australian College of General Practitioners (RACGP), the electronic Therapeutic Guidelines (eTG) and Department of Health and Ageing, four state-level Department of Health guidelines (Quit for New Life, NSW Health, Queensland Health and Western Australia Department of Health), three additional guidelines by Alfred Health (June, 2017 and Aug 2017 updated) and the Royal Women's Hospital, Victoria (referred herein as the Women's). The Cancer Council Victoria published a comprehensive review of smoking cessation, and whilst not a clinical guideline per se, has been included as a key document.
- The international guidance documents included guidelines from New Zealand, UK, Canada and the US.
- The quality grading of evidence and strength of the guidelines were assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument (**Error! Reference source not found.**). Two national (RACGP and Cancer Council Victoria) and two international guidelines (NZ and UK) were assessed as higher quality. Several other national guidelines were also considered very good quality including ACT Health, WA Health, NSW Health, Alfred Health (updated guidelines – 2020), eTG, Department of Health and Ageing, and the Women's, along with the remaining two international guidelines (Canada and US).
- Several similarities were apparent between the national and international guidelines as follows.
 - Approach to smoking cessation, including choice of pharmacotherapy, should be tailored to the patient including consideration of nicotine dependence, clinical suitability, and patient preference.
 - Varenicline was considered more effective than NRT monotherapy and bupropion, and at least equivalent to combination NRT.
 - Combination NRT was considered more effective than monotherapy NRT or bupropion.
 - Any pharmacotherapy combined with behavioural support was considered more effective than pharmacotherapy alone.

- Referral to a specialised counselling service (e.g. Quitline or similar trained smoking cessation counsellors) was recommended.
- Using appropriate dosing for NRT, proportional to the level of nicotine dependence, was important, as was up-titrating the dose (including the option of double patching i.e. adding an extra patch) if there was limited response. Under-dosing was considered common and associated with risk of not achieving cessation.
- NRT should be used for 8 - 12 weeks, varenicline for 12 weeks and bupropion for at least 7 weeks. Some national and international guidelines allowed for a second course of NRT or varenicline, but not bupropion, to prevent relapse, or if complete abstinence was not achieved.
- NRT was considered appropriate for use in adolescents > 12 years, patients with stable CVD and pregnant women (although preference was to achieve smoking cessation without use of NRT in pregnant women).
- There were some discrepancies between various guidelines, particularly around the use of combinations of NRT, varenicline and bupropion. Some guidelines recommended some or all combinations, but the UK specifically recommended against the combination of varenicline and bupropion.
- Differences were also seen in how nicotine dependence was assessed, particularly in relation to dosing of NRT. However, there was agreement on the overall principle that increased reliance on nicotine (whether measured by time to first cigarette, or number of cigarettes per day, or a combination of these) should trigger use of higher doses of NRT at the time of quitting.

RQ 2: Compare TGA indications and PBS restrictions to the most clinically relevant clinical guidelines identified in RQ1

- All guidelines recommendations were within TGA indications for all therapies under consideration (NRT, bupropion and varenicline).
- The PBS listing for NRT does not provide for the use of two forms of NRT at once (i.e. no combination therapy) which is inconsistent with all guidelines reviewed and TGA-approved dosing of NRT.
- The PBS listings for varenicline and bupropion were consistent with guideline recommendations for use of these drugs as monotherapy. However, the PBS restriction of requiring a six-month gap between initiating sequential quit attempts was not reflected in the guidelines.
- The PBS listings for varenicline and bupropion are inconsistent with the guidelines that support the use of these therapies in combination with another smoking cessation therapy. However, there was also discrepancy between guidelines as to whether these medications should be used in combination. The TGA indications do not preclude combination therapy.
- Cut-down to quit and pre-quit use of NRT were TGA-approved and recommended strategies in most guidelines. This approach was not explicitly considered in the PBS restrictions, and may not be adequately accounted for within the allowable quantities and repeats.
- Current PBS prescriptions for NRT do not allow for extension of a course of therapy beyond 12 weeks although several guidelines recommended extension of therapy if

needed. The exception to this was for Aboriginal and Torres Strait Islander populations where up to 24 weeks of NRT were allowed. No guideline distinguished between Aboriginal and Torres Strait Islander populations and general populations regarding extension of therapy.

- The allowable quantities for NRT patches in the current PBS restrictions do not account for 'double-patching' although several guidelines suggested that this may be useful for heavily dependent smokers.
- Higher strength NRT patches were listed for Aboriginal and Torres Strait Islander populations but lower strength patches were not. This was inconsistent with the guidelines which do not indicate any evidence-based requirement for only higher strengths for Aboriginal and Torres Strait Islander populations.

RQ 3: Review the most commonly recommended clinical assessment measure used to evaluate the severity of nicotine dependence

- Under-dosing of NRT was considered common and assessment of nicotine dependence was recommended prior to prescribing of pharmacotherapy.
- Clinical guidelines used a range of instruments to assess nicotine dependence including:
 - The Fagerström test which tests psychological and physiological dependence
 - A subset of two of the Fagerström questions – 'how long until you have your first cigarette after waking?', and 'how many cigarettes a day do you smoke?'
 - Simply asking 'how many cigarettes a day do you smoke?'

Stakeholder views (Forum and public consultations)

Initial consultation feedback recommended that health service guidelines be included in the evaluation of ToR 1, in addition to national and international guidelines. Based on this feedback several health service guidelines, including those published by Alfred Health and the Royal Women's Hospital (Victoria), have been included in the evaluation of ToR 1. A review published by the Cancer Council Victoria was included as a 'key document.'

Stakeholders generally considered that the PBS restrictions should align with current clinical guidelines (such as the RACGP's 'Supporting smoking cessation: A guide for health professionals').

Stakeholders considered it important to ensure that the availability of medicines for smoking cessation are subsidised consistent with clinical guidelines to support people to quit smoking.

1.2 Methodology and identification of relevant guidelines

1.2.1 General approach

The following approach was used to address ToR 1:

1. Identify key relevant clinical guidelines for smoking cessation therapy, including both national and international guidelines via targeted online searching.
2. Document current TGA indications and PBS restrictions for smoking cessation therapy and compare to the recommendations of the identified clinical guidelines including recommendations for specific populations of interest (i.e. Aboriginal and Torres Strait Islander people, pregnant/breast feeding women, Incarcerated persons, people with co-morbidities (alcohol/substance abuse, cardio vascular risk factors, previous smoking related illness) and any other high-risk group identified in clinical guidelines.
3. Review the most common clinical assessment measures used to evaluate the severity of nicotine dependence and any related recommendations for dosage of the PBS-listed treatments.

1.2.2 Medicines of interest

There were three PBS-listed medicines for smoking cessation:

- Nicotine replacement therapy (NRT)
- Varenicline
- Bupropion

1.2.3 Key outcomes

Comparison of recommendations around:

- Use of smoking cessation therapies as monotherapy vs combination therapy
- Use of smoking cessation therapies in combination with behavioural therapy and whether certain types of behavioural therapy are recommended.
- Dosing of smoking cessation therapies in relation to intensity of smoking
- Use of smoking cessation therapies in specific populations of interest.

1.2.4 Inclusion/Exclusion Criteria

- The most recent version of each available clinical guideline was included.
- For national guidelines, a range of guidelines across different health services were included to maximise identifying locally relevant advice.

- For international guidelines, only country-level guidelines aimed at the general population, from the United Kingdom (UK), United States of America (US), New Zealand and Canada were included.
- Clinical guidelines where smoking cessation was only part of a guideline on a different topic (e.g., a paragraph on tobacco treatment within a guideline for asthma or COPD) were excluded.
- No clinical guidelines were excluded based on the quality assessment.

1.2.5 Search strategy

For Australian guidelines, the search covered Department of Health sites and local jurisdictions, as well as any known guidelines from previous PBAC reviews and submissions to the post marketing review. The search was limited to the latest clinical guidelines published. For international guidelines, the search covered all Department of Health websites and similar within specific countries of interest: New Zealand, Canada, United States and the United Kingdom.

A supplementary search of guideline databases ([Australian Clinical Practice Guidelines Portal](#), [Guidelines International Network](#), [Scottish Intercollegiate Guidelines Network](#)) using the terms “tobacco” “smoking” and “smoking cessation”, and a PubMed search (((“Smoking Cessation Agents”[Mesh] OR “Smoking Cessation Agents” [Pharmacological Action]) AND “Smoking Cessation”[Mesh]) AND (“Practice Guidelines as Topic”[Mesh] OR “Practice Guideline” [Publication Type])) was also undertaken.

1.2.6 Selection and screening of guidelines

Clinical guidelines were reviewed to assess eligibility of national and international guidelines based on the determined inclusion and exclusion criteria.

1.2.7 Data extraction

Data were extracted using a pre-determined data extraction form. Key data included year of development, who developed it and the methodology, key recommendations around use of NRT, bupropion, varenicline and behavioural therapy including dose, dosage form and length of treatment, combination treatment, as well as any specific guidance for populations of interest.

1.2.8 Quality assessment

The quality grading of evidence and strength of clinical guidelines recommendations were assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.

1.3 Clinical guidelines identified for ToR1

Twelve national (Australian) and four international guidelines were identified as being relevant to this review. National guidelines included three country-level guidelines from: The Royal Australian College of General Practitioners (RACGP), the electronic Therapeutic Guidelines (eTG), and the Department of Health and Ageing; four state/territory level Department of Health guidelines (Quit for New Life, NSW Health, Queensland Department of Health, ACT Health and WA Health); three additional guidelines by Alfred Health (June, 2017 and August 2017 update) and the Royal Women's Hospital, Victoria (herein referred to as the Women's); an additional review document by Cancer Council Victoria was also included to supplement identified clinical guidelines. The international guidelines were from New Zealand, UK, Canada and US. Summaries of the national and international guidelines are presented in Table 1 and Table 2.

Several of the national guidelines (RACGP, eTG, QFNL, NSW Health, Department of Health and Ageing, Alfred Health and Cancer Council Victoria) provided guidance for primary care or general settings, with others (ACT Health, WA Health, the Women's, Qld Health and Alfred Health (updated)) giving special focus to hospital-based health services. All of the identified international guidelines targeted general or primary-care based settings except for the US which specified it was for primary health services.

All the guidelines, except for QFNL, the Women's and Department of Health and Ageing, were written for general populations, although several contained qualifications or specific advice for specific populations such as pregnancy/breastfeeding or adolescents.

Two guidelines were specifically developed to provide advice for Aboriginal and Torres Strait Islander populations (QFNL and Department of Health and Ageing), and two documents (QFNL and the Women's) were only addressing smoking cessation in pregnancy.

1.3.1 National guidelines

The twelve identified national guidelines were:

- RACGP clinical guidelines, "Supporting Smoking Cessation: A Guide for Health Professionals, second edition", 2019: The RACGP first developed 'Supporting smoking cessation: 'A guide for health professionals'' in 2011. Since then, there were two minor updates in 2012 and 2014. This second edition was the most comprehensive update. It also incorporated the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) framework for assessment of clinical evidence and drafting of practice recommendations.
- Government of Western Australia, Department of Health: "Guidelines to manage nicotine withdrawal and cessation support in nicotine dependent patients", 2020. This guideline provided information on how to manage WA Health patients with nicotine dependence and support those wanting to quit while in hospital.
- Queensland Health, "Smoking Cessation, Clinical Pathway", 2017: This tool was for screening smoking behaviour and to guide support for those who temporarily could not smoke or wish to reduce/quit smoking.
- NSW Ministry of Health, "Managing Nicotine Dependence: A Guide for NSW Health Staff", 2015: The primary purpose of this Guide was to support NSW Health staff to

provide effective, evidence-based treatments for nicotine dependent clients including routine brief interventions for smoking cessation to all clients who smoke or are recent quitters. Settings included all NSW Health facilities – hospital inpatient and outpatient facilities, primary and community care, dental, eye care and pharmacies.

- Cancer Council Victoria, “Tobacco in Australia: Facts and Issues, A Comprehensive Online Resource”, 2020: This guidance document provided a comprehensive review of the major issues in smoking and health in Australia, compiled by the Cancer Council Victoria. Production of editions 2 to 4 of this publication was funded by the Australian Government Department of Health and Ageing. Ongoing updates were being funded by the Australian Government Department of Health, with contributions from Cancer Councils in all states and territories, Quit, NSW Health, ACT Health, and ACOSH.
- Alfred Health-updated: This update provided a specific update on prescribing of smoking cessation medication for inpatients and was a partial update of the next guideline (Alfred Health).
- Alfred Health, “An ABCD approach to supporting people who smoke; A guide for health services”, 2017. The guide’s aim was to be a practical, concise and evidence-based resource to be used by a wide range of health professionals working with people who smoke. This guideline and the previous one (Alfred Health-updated) were together considered as one guideline for the purposes of this review.
- Quit for New Life, “Protocol for the provision of Nicotine Replacement Therapy”, 2017: This protocol described the procedure for the provision of Nicotine Replacement Therapy (NRT) to nicotine dependent antenatal and postnatal Aboriginal women and women who identified as having an Aboriginal baby (and their cohabitants) who are participating in the Quit for New life (QFNL) program. The protocol was applicable to all participating Aboriginal Maternal and Infant Health Services (AMIHS) and Building Strong Foundations for Aboriginal Children, Families and Communities (BSF) programs and other antenatal and postnatal services that were implementing the QFNL program.
- eTG Complete, “Smoking Cessation”, 2020: eTG is an independent, not for profit organisation providing comprehensive clinical guidelines to clinicians on a broad range of topics.
- Department of Health and Ageing, “Medicines to help Aboriginal and Torres Strait Islander people stop smoking: A guide for health workers”, 2012: This guidance document was a part of the “Tackling Indigenous Smoking and the Closing the Gap in Indigenous Health Outcomes” initiative of the Australian Government.
- The Women's (The Royal Women's Hospital, Victoria), “Supporting smoking cessation during pregnancy - nicotine replacement therapy (NRT)”, 2020: This guideline described the prescribing and administration of nicotine replacement therapy (NRT) to aid cigarette smoking cessation during pregnancy, and was intended for use by all staff involved in the clinical management of pregnancy.
- ACT Health, “Managing Nicotine Dependence”, 2018: This guideline provided a standardised procedure for managing nicotine dependence in patients admitted to any ACT Health facility. It was intended for use by all staff in ACT Health who had a role in managing nicotine dependence in patients or staff.

1.3.2 International Guidelines

The four identified international guidance documents were:

- Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment (CAN-ADAPTT), “Canadian Smoking Cessation Clinical Practice Guideline”, published in 2012, pharmacotherapy section updated in 2018: The intended end users of this guideline were Canadian healthcare providers across a diverse range of clinical or treatment settings. The primary CAN-ADAPTT clinical practice guideline provided guidance on Counselling and Psychosocial approaches as well as specific guidance around smoking cessation in Aboriginal peoples, hospital-based populations, people with mental illness, pregnant and breastfeeding women, and youth (children and adolescents). It was supplemented by the ‘Algorithm for tailoring pharmacotherapy’ which was separately updated in 2018 and both these together were considered as one guideline for the purposes of this review.
- U.S. Preventive Services Task Force, “Behavioural and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement”, 2015: This guidance document, aimed at all clinicians, was an update of the 2009 U.S. Preventive Services Task Force (USPSTF) recommendation on counselling and interventions to prevent tobacco use and tobacco-related disease in adults, including pregnant women.
- New Zealand Government, Ministry of Health, ‘Background and Recommendations of The New Zealand Guidelines for Helping People to Stop Smoking’, 2014: This Guideline, aimed at all healthcare workers, replaced the New Zealand Smoking Cessation Guidelines, which were published in 2007. The update was based on recommendations from a recent review of the effectiveness and affordability of interventions for stopping smoking (West et al 2013), supplemented with information from the literature review undertaken to produce the 2007 Guidelines (Ministry of Health, 2008). The main guideline was supplemented by the ‘Guide to prescribing nicotine replacement therapy’, also published in 2014, and these two documents were considered as one guideline for the purposes of this review.
- National Institute for Health and Care Excellence (NICE), UK. “Smoking cessation interventions and services”, 2018. This guideline was aimed at a wide range of end-users including providers of stop smoking interventions or services, health/social and other frontline staff of stop smoking services, health and wellbeing boards, as well as members of the public who wish to stop smoking. The guideline was a partial update of NICE guidelines on brief advice and referral for smoking cessation (PH1) and smoking cessation services (PH10) and was supplemented by specific advice provided in the British National Formulary around prescribing of pharmacotherapy. Both these documents together were considered as one guideline for the purposes of this review.

1.3.3 Quality Assessment of the identified guidelines

The quality grading of evidence and strength of the guidance documents were assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. The AGREE II consists of 23 key items organized within 6 domains followed by 2 global rating

items (“Overall Assessment”). Each domain captures a unique dimension of guideline quality. The overall rating of guidance documents is presented in Table 1 and Table 2, with the detailed assessments provided in Table 13 and Table 14 in the Appendix.

Two national guidance documents were considered of higher quality; RACGP and Cancer Council Victoria, along with two international guidelines (NZ and UK). Several other national guidelines were also considered very good quality including ACT Health, WA Health, NSW Health, Alfred Health (updated guidelines – 2020), electronic Therapeutic Guidelines, Department of Health and Ageing, and the Women’s along with the remaining two international guidelines (Canada and US).

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Table 1: Summary of Identified Clinical Guidelines - National

Organisation	Year	Health service setting / Target audience	Pharmacotherapy included	Behavioural support	Development methodology/evidence synthesis	Basis for recommendations	AGREE II overall quality rating	Reference
RACGP	2019	Wider primary care setting / All HCP supporting people wishing to quit	NRT VAR BUP	Yes	GRADE evidence review	6-week stakeholder consultation process Quality of evidence (high, moderate, low, very low) Strength of recommendation (strong, weak, conditional)	7	(1)
ACT Health	2018	All ACT Health facilities, primarily hospital inpatient settings.	NRT	No	Developed by ACT Health, Canberra Hospital and Health Services.	Not stated.	6	(2)
WA Health	2020	Hospital/ Clinical staff caring for inpatients with nicotine dependence	NRT	No	Based on 'best practice for smoking cessation and nicotine withdrawal management'	Not stated.	5	(3)
QLD Health	2017	All state acute, community, dental and mental health settings/ clinicians	NRT VAR (limited) BUP (limited)	Yes	Expert review of clinical evidence to develop clinical pathway	Consultation with clinicians, consumers, Quitline representatives, preventive health over several months	5	(4)
NSW Health	2015	All NSW Health facilities/ NSW Health staff	NRT VAR	Yes	Update of previous guidance documents	Consultation with LHDs, NSW Health and the Australian Association of	6	(5)

			BUP NOR			Smoking Cessation Professionals		
Cancer Council Victoria	2020	All	NRT VAR BUP NOR CLO CYT	Yes	Not stated	Not stated	7	(6)
Alfred Health	2017	All health professionals working with people who smoke	NRT VAR BUP	Yes	Literature review	Not stated	5	(7)
Alfred Health- updated version	2020	All Alfred Health staff involved in providing care for patients who smoke.	NRT	Yes	Literature review	Not stated	6	(8)
QFNL	2017	Services implementing the QFNL program; All healthcare staff assessing and providing NRT to women and cohabitants QFNL programs /	NRT	No	Literature review of national and state guidance	Not stated	4	(9)

Therapeutic Guidelines	2020	All	NRT VAR BUP	Yes	Latest international literature	Expert group consensus	6	(10)
Department of Health and Ageing	2012	All health workers	NRT VAR BUP	Yes	Literature review	Not stated	6	(11)
The Women's	2020	All staff involved in the clinical management of pregnancy.	NRT	Yes	Literature review	Consultation of clinicians and other stakeholders, particularly QUIT Victoria	6	(12)

Abbreviations: ACT = Australian Capital Territory; NSW: New South Wales; QLD = Queensland; WA = Western Australia; NRT = Nicotine replacement therapy; VAR = Varenicline; BUP = Bupropion; NOR = Nortriptyline; CLO = Clonidine; CYT = Cytisine; HCP = Healthcare Provider; RACGP = Royal Australian College of General Practitioners; QFNL = Quit for New Life; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; LDH = Local Health Districts; AGREE II = Appraisal of Guidelines for Research & Evaluation II (overall guidelines assessment score takes into account the appraisal items considered in the AGREE II assessment with score 1 = lowest possible quality, and score 7 = highest possible quality).

Table 2: Summary of Identified Clinical Guidelines – International

Guidance document	Year	Health service setting / Target audience	Pharmacotherapy included	Behavioural support	Development methodology/evidence synthesis	Basis for recommendations	Overall AGREE II score	Reference
CAN-ADAPTT	2018	All settings/ Canadian healthcare providers	NRT VAR BUP NOR CLO CYT	Yes	ADAPTE process – existing guidelines identified, reviewed by four reviewers using AGREE	Clinical guidelines development group, Key recommendations extracted; grades of recommendations and levels of evidence using modified GRADE.	6	(13, 14)
U.S. Preventive Services Task Force	2011	Primary care	NRT VAR BUP	Yes	Review of systematic reviews including public consultation on methodology	Good-quality, fair-quality, or poor-quality;	6	(15)
New Zealand guidelines for helping people to stop smoking	2014	All settings	NRT VAR BUP NOR	Yes	Updated literature review	NHMRC hierarchy of evidence	7	(16, 17)
NICE stop smoking	2018	All settings	NRT VAR	Yes	NICE guidelines development methodology	GRADE approach plus cost-effectiveness evidence review	7	(18)

interventions and services			BUP					
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Abbreviations: NRT = Nicotine replacement therapy; VAR = Varenicline; BUP = Bupropion; NOR = Nortriptyline; CLO = Clonidine; CYS = Cytisine; CAN-ADAPTT = Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment; NICE = National Institute for Health and Care Excellence; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; NHMRC = National Health and Medical Research Council; AGREE II = Appraisal of Guidelines for Research & Evaluation II – (overall guidelines assessment score takes into account the appraisal items considered in the AGREE II assessment with score 1 = lowest possible quality, and score 7 = highest possible quality).

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1.4 RQ1: Comparison of Clinical guidelines

1.4.1 National guidelines

Table 3 presents a summary of the key recommendations in the national guidelines included in this review.

1.4.1.1 Nicotine replacement therapy (NRT)

All national clinical guidelines included in this review included NRT in their recommendations. In all guidelines, NRT was recommended for all people who smoke and/or those who have evidence of nicotine dependence.

Two guidelines, Quit for New Life (QFNL) and the Women's, solely considered NRT for smoking cessation due to their focus on pregnancy. Both these guidelines recommended NRT only be used in women unable to achieve abstinence using non-pharmacological approaches and where the benefits of non-smoking outweighed the risks of NRT.

Additionally, several hospital-based guidelines (Alfred Health update, ACT Health, Qld Health) also provided guidance predominantly around NRT which was related to their focus on inpatient management of patients. In these hospital settings, they included advice for patients who may or may not wish to quit, and therefore included the goal of relieving nicotine withdrawal rather than solely assisting with quitting.

Dosage form, dose, and length of therapy

All forms of NRT were considered across the guidelines. This included continuous-use or long-acting formulations (transdermal patches), and intermittent-use or short-acting formulations (gum, lozenge, inhalator, mouth spray, strips). The intermittent-use NRT formulations (gum, lozenge, inhalator, mouth spray, strips) were preferred in the QFNL and the Women's guidelines over continuous-use formulations (transdermal patches) for pregnant and postnatal women because they provide smaller daily doses of nicotine than the latter. The intermittent-use forms were also recommended for patients who were allergic to patches (QLD Health).

Table 4 summarises the dosage recommendations for NRT within the included guidelines. Across the guidelines, the dose of NRT recommended was generally relative to the level of nicotine dependence. However, some guidelines were more prescriptive than others. For instance, WA Health recommended type and dose of NRT to be provided (short acting vs patch vs combination) on the basis of the Fagerström score, in contrast to Qld Health and QFNL which recommended titration of NRT to "achieve" effect, and ACT Health which advised to offer combination NRT to patients that were nicotine dependent. The QFNL and Women's guidelines also advised removing transdermal patches at night to allow an eight-hour break in therapy before the new patch was applied the next morning.

RACGP guidelines recommended a higher dose of oral NRT (i.e. 4 mg gum and lozenge) and patches (21 mg/24-hour patch and 25 mg/24-hour patch) for those who smoke with higher

nicotine dependence but also for those with less nicotine dependence but who continue to report cravings when using the weaker strength. This was consistent with information provided in the Cancer Council Victoria review that was based on a recent Cochrane review (2019) ⁽¹⁹⁾ which affirmed a higher likelihood of successful quitting if higher-dose compared with lower-dose nicotine patches or nicotine gum were used.

Underdosing of NRT was acknowledged as a common yet preventable issue in the RACGP and NSW Health guidelines. Several guidelines (RACGP, QLD Health, NSW Health, Alfred, Department of Health and Ageing and ACT Health) recommended the use of multi-patching and/or extra oral NRT products to manage withdrawal symptoms rather than resort to smoking given over-dosing was rare on NRT. Furthermore, the RACGP guidelines noted that standard dosing references and product information guides for NRT tended to recommend more conservative doses.

The standard length of NRT treatment across the guidelines was between 8 and 12 weeks. Most of the guidelines; RACGP, NSW Health, Alfred Health, and Department of Health and Ageing recommended the use of NRT for at least 8 weeks, while the QFNL guidelines recommending each woman be offered up to 12 weeks supply of NRT in total per quit attempt. Unlike QFNL, the Women's guidelines aimed at discontinuation of NRT and quitting within 6 to 8 weeks of commencing NRT or for the shortest duration possible to minimise fetal exposure to nicotine. Some guidelines such as QLD Health recommended the use of NRT for only 2 weeks before reassessment. WA Health and ACT Health recommended the supply of a minimum of 7 days of NRT for those who chose to remain abstinent, reflecting the likely restrictions on supplying medicines in an acute setting, but noted that a standard course of NRT was 12 weeks with evidence indicating that 8 weeks of NRT treatment was as effective as 12 weeks.

RACGP guidelines indicated limited evidence of benefit from longer term NRT; this was based on two RCTs that compared the standard course of treatment (8 weeks) with a longer course of treatment (up to 52 weeks) but found no significant effect from the longer course. Despite acknowledging this lack of evidence, the RACGP, Alfred Health, Cancer Council Victoria, and the Department of Health and Ageing acknowledged that an extended (but not limitless) period of treatment may be reasonable for some patients, with the RACGP guidelines noting that the prospect of stopping may be confronting for some patients after 24-weeks of therapy (i.e. after which there is no evidence of efficacy). The Department of Health and Ageing guidelines highlighted that a few smokers may need to use NRT for months or even years to quit cigarettes.

All guidelines except WA Health, QLD Health, QFNL and ACT Health acknowledged the potential benefit of the use of NRT for 2 weeks or more prior to the set quit date and/or "cut-down-to quit" approaches for people not yet willing to quit, with the expectation for cessation within 6 months noted in the eTG.

The RACGP, Alfred Health, and the Women's guidelines did not recommend tapering or weaning doses over a period of weeks which was also reiterated in the Cancer Council Victoria guidance. The eTG noted that patches could be stopped abruptly or tapered but

recommended that short acting forms be gradually reduced. ACT Health explicitly recommended tapering of NRT.

Monotherapy versus combination therapy

All national guidelines recommended the use of combination NRT for smoking cessation stating that combination NRT (i.e. patch and oral form) was more effective for some than monotherapy. However, NSW Health guidelines also indicated that for less nicotine dependent clients, the use of a patch or a single form of oral NRT may be sufficient to manage the urge to smoke and control withdrawal symptoms.

Some guidelines, (RACGP, QLD Health, NSW Health, Alfred Health (2017), QFNL, the Women's, and eTG) recommended combination NRT be offered to people who were unable to remain abstinent or who continued to experience cravings and withdrawal symptoms using one type of NRT. WA Health, the Women's, and QFNL guidance documents specifically recommended combination NRT only for patients with moderate or high levels of nicotine dependence. ACT Health recommended all patients who were nicotine dependent be offered combination NRT.

Behavioural support

Most of the national guidelines specifically indicated that pharmacotherapy was more effective when accompanied by behavioural support. The Department of Health and Ageing, WA Health, QLD Health and ACT Health guidelines did not specifically mention the impact on efficacy with behavioural support but did recommend providing patients with information about services which provided behavioural support such as Quitline or the Local Cancer Council WA Fresh Start program. Although QFNL did not provide any narrative around behavioural therapy, NRT in that program was provided as part of a broader package of interventions including referral to Quitline.

The Women's guidelines specifically recommended non-pharmacological interventions such as multi-session behavioural interventions (for example, as delivered by Quitline) as first-line therapy for pregnant women.

Relapse prevention

The RACGP guidelines were the only guidelines recommending an additional course of NRT at the end of a standard course of NRT to prevent relapse events, however the strength of this recommendation was graded of low certainty. This was supported by the Cancer Council Victoria guidance.

Treatment failure/ switching

There was no explicit recommendation around the clinical pathway for people who failed treatment with NRT or switched between therapies for sequential quit attempts.

1.4.1.2 Varenicline

Six national guidelines included varenicline (RACGP, NSW Health, Alfred Health, Cancer Council Victoria, eTG and Department of Health and Ageing) with most recommending varenicline as the most effective monotherapy because of evidence generally showing superiority to bupropion and single forms of NRT. The Department of Health and Ageing guideline noted that although evidence suggested that varenicline was the most effective medicine to quit smoking, it had not been trialled specifically among Aboriginal or Torres Strait Islander people. Varenicline was generally considered equally effective as combination NRT.

QLD Health only recommended varenicline for patients currently using varenicline upon hospital admission, with the provision of NRT offered to inpatients if varenicline was not available. .

Dose forms, dose and length of treatment

Varenicline was only available in an oral form. RACGP, WA, and Cancer Council Victoria guidance referred to the standard dose set out in the approved prescribing information noting the need for dose reduction in people with severe renal impairment or to minimise dose-related adverse effects. The duration of treatment was 12 or 24-weeks (see “Relapse Prevention” below). The RACGP guidelines also provided two treatment strategies, fixed and flexible. The fixed option involved setting a date to stop smoking with treatment initiated one to two weeks before this date. The flexible approach involved initiating varenicline dosing while still smoking, with smoking cessation occurring between days 8 and 35 of treatment. Both options were considered equally effective and choice a matter of patient preference. However, the Cancer Council Victoria review noted limited evidence that suggested an increased risk of relapse when quitting was delayed while using varenicline, highlighting that an extended duration of varenicline use may be beneficial under such circumstances.

Monotherapy versus combination therapy

Most national guidelines recommended the use of varenicline as monotherapy. The eTG stated there was no conclusive evidence to support combining varenicline with NRT to improve rates of smoking cessation. However, the RACGP recommended the use of varenicline in combination with NRT for people who were attempting to quit smoking using varenicline alone accompanied by behavioural support, and the Cancer Council Victoria review highlighted evidence for improved effectiveness compared to varenicline monotherapy. The RACGP guideline graded the evidence for this recommendation of moderate certainty.

Regarding the combination of varenicline with bupropion, the Cancer Council Victoria review highlighted evidence demonstrating greater efficacy for combination bupropion and varenicline compared to varenicline alone.

With or without behavioural support

As for NRT, most national guidelines considered pharmacotherapy generally more effective when accompanied by behavioural support, and either specifically recommended

behavioural therapy with varenicline, or recommended providing information to patients about behavioural support services such as Quitline.

RACGP was the only guideline to explicitly specify, with high certainty based on the available evidence, that varenicline should be provided in combination with behavioural support.

Relapse Prevention

The RACGP, NSW Health, Alfred, eTG and Department of Health and Ageing guidelines recommended that a further course of varenicline at the end of a standard course may be of benefit in preventing relapse events in people who had successfully quit smoking on varenicline. This was supported by the Cancer Council Victoria review. However, the expert advisory group developing the RACGP guidelines rated the certainty of evidence as low.

Treatment failure/ switching

No national guideline provided recommendations around treatment failure nor switching between therapies in case of a failed quit attempt. No guideline discussed or recommended gaps between consecutive courses of varenicline or other therapies used for subsequent quit attempts.

1.4.1.3 Bupropion

Seven guidelines in some way included bupropion in their recommendations with four guidelines considering bupropion less effective than varenicline, but a useful option when varenicline was not appropriate (RACGP, NSW health, eTG, and Alfred Health). This perspective was supported by the Cancer Council Victoria review. The eTG guideline noted that bupropion had similar efficacy to NRT in aiding smoking cessation, and this was also supported by the Cancer Council Victoria review. The QLD Health guidelines recommended bupropion only for patients who were currently using this medication prior to hospital admission, and provision of NRT if bupropion was not available.

The Cancer Council Victoria review stated there was high quality evidence showing that bupropion increased the likelihood of long-term smoking cessation compared to placebo; a conclusion from a Cochrane review published in 2014.

Dose forms, dose and length of treatment

The only available dosage form of bupropion was oral. All guidelines recommended dosing according to the approved product information, with a recommended dose of bupropion of 150 mg/day for the first three days, then increased to 150 mg twice per day with patients recommended to stop smoking in the second week of treatment.

The RACGP guideline noted that under PBS rules, a maximum of nine weeks of PBS-subsidised treatment with this drug was permitted per 12-month period. In this guidance, an initial prescription for two-weeks supply was recommended, with follow-up monitoring thereafter for progress and adverse events (skin rash, neuropsychiatric symptoms,

insomnia). Furthermore, encouraging patients to complete at least 7 weeks of therapy was recommended.

Monotherapy versus combination therapy

Most of the guidelines recommended bupropion as a monotherapy due to insufficient evidence to support combination of bupropion with either NRT or varenicline (RACGP, NSW Health, and eTG).

The Cancer Council Victoria review indicated there was evidence that suggested the combination of bupropion and NRT was more effective than either medication alone, but also noted other evidence that did not find additional benefit of this combination.

With or without behavioural support

Most national guidelines considered pharmacotherapy more effective when accompanied by behavioural support. This recommendation was not specific for bupropion but was applicable for all pharmacotherapies.

Relapse prevention

No national guidelines provided any recommendation around relapse prevention when using bupropion as a treatment for smoking cessation.

Treatment failure/ switching

No national guidelines provided recommendations around treatment failure nor switching between therapies. Additionally, there were no recommendations around gaps between different treatments in the case of failure to achieve cessation.

1.4.1.4 Behavioural Support – a closer look

Most national guidelines indicated that pharmacotherapy was more effective when accompanied by behavioural support, although no guidelines provided recommendations about the specific type or duration of the behavioural therapy, limiting advice to recommending referral to a specialist provider such as Quitline. However, some guidelines provided some narrative around the behavioural therapies which could potentially be used in combination with pharmacotherapy. These are summarised in Table 5.

The Cancer Council Victoria review provided a thorough review of all the different types of counselling available including evaluation of mode of delivery (face to face, telephone, internet, paper copies etc.) noting that efficacy for all these modes of delivery had been demonstrated however efficacy was dependent on patients access and utilisation of such services.

RACGP recommended pharmacotherapy combined with behavioural support as the most effective first line option to maximise the chances of quitting.

The Women's guideline recommended non-pharmacological interventions such as multi-session behavioural intervention (for example, as delivered by Quitline) as sole first-line therapy for pregnant women. Pharmacotherapy (NRT) in conjunction with behavioural

intervention was only recommended for consideration if women were unable to achieve abstinence using non-pharmacological interventions alone or in those with moderate to high nicotine dependence.

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Table 3: Summary of Key Recommendations Included in National Guidelines

Recommendation	RACGP	WA Health	QLD Health	NSW Health	Cancer Council Victoria	Alfred Health	QFNL	eTG	DOHA	The Women's	ACT Health
Overall											
Approach to smoking cessation, including choice of pharmacotherapy should be individualised based on nicotine dependence, clinical suitability, and patient preference.	√	√	√		√			√			√
Any form of pharmacotherapy is more effective with behavioural support.	√			√	√	√ (NRT)		√			
Efficacy											
Combination nicotine replacement therapy (NRT) (i.e. patch and oral form) was considered more effective than NRT monotherapy.	√	√	√	√	√	√	√	√	√	√	√
Varenicline was considered the most effective form of single pharmacotherapy	√			√	√	√			√		
Varenicline was considered equivalent to NRT combination therapy	√			√	√	√					
Bupropion was considered less effective than varenicline	√			√	√	√		√			
Dosage											

Dose of NRT should be based on assessment of nicotine dependence	√	√	√					√	√	√	
Higher dose therapy with NRT patch is possible by adding a second patch (i.e. multi-patching)	√		√	√		√			√		√
NRT patches do not need to be tapered at the end of treatment	√				√	√		√		√	
Pre-quit or cut-down to quit NRT use may be useful	√			√	√	√		√	√	√	
Varenicline could be used in combination with NRT for people attempting to quit smoking using varenicline and behavioural support	√				√						
Extension of treatment											
Longer durations of treatment may be required in highly dependent smokers	√				√	√			√		
For people who have stopped smoking at the end of a standard course of NRT, clinicians may consider an additional course of NRT	√				√						
After a standard course of varenicline, an additional course of varenicline could be considered to reduce relapse for people who have abstained from smoking or haven't yet achieved cessation due to an initial delay in quitting.	√			√	√	√		√	√		
Special Populations											

NRT can be used in adolescents > 12 years	√			√	√	√	√		√		√
NRT is safe in stable CVD	√			√		√			√		√
NRT can be used in pregnant women if unable to quit without assistance				√		√	√		√	√	√

Table 4: NRT Dosing Recommendations in National Guidelines

Guideline	Dose recommendation
RACGP	<p>Use all below for up to 12 months, but limited evidence for effectiveness longer than 24 weeks.</p> <p>Smokes > 30 min from waking and <10 CPD: 2mg or 1.5mg lozenge, OR 2mg gum, OR 1 mg spray, OR 15mg inhaler</p> <p>Smokes > 30 min from waking and > 10 CPD: 21mg/24 hr patch, PLUS 2mg gum, OR 2mg/1.5mg lozenge, OR 1 mg spray, OR 15mg inhaler</p> <p>Smokes < 30 min from waking and <10 CPD 21mg/24hr patch, PLUS 2mg gum, OR 2mg/1.5mg lozenge, OR 1mg spray, OR 15mg inhaler</p> <p>Smokes < 30 min from waking and > 10 CPD 21mg/24h patch, PLUS 4mg gum, OR 4mg lozenge, OR</p>

	<p>1mg spray, OR 15mg inhalator</p>
WA Health	<p>Low Fagerström score = 1 - 4 Gum, inhaler or lozenge (used intermittently)</p> <p>Moderate Fagerström score = 5 - 6 Patch</p> <p>High Fagerström score = 6+ Patch (combination if necessary)</p>
Queensland Health	<p>21mg/24hr patch, PLUS Gum/lozenge/inhalator or spray</p> <p>If not effective, add a second 21mg/24hr patch.</p> <p>Continue 1 x patch and gum/lozenge/inhalator or spray for 8 – 12 weeks after smoking cessation.</p>
NSW Health	<p>All below regimens for > 8 weeks</p> <p>Smokes > 30 min from waking and <10 CPD: 14mg/24h patch or 10mg/16hr patch, PLUS 2mg or 1.5mg lozenge, OR 2mg gum</p> <p>Smokes > 30 min from waking and > 10 CPD: 21mg/24 hr patch or 25mg/16hr patch, PLUS 2mg gum, OR 2mg/1.5mg lozenge</p> <p>Smokes < 30 min from waking and <10 CPD 14mg/24h patch or 10mg/16hr patch, PLUS 2mg gum, OR 2mg/1.5mg lozenge, OR</p> <p>Smokes < 30 min from waking and > 10 CPD 21mg/24h patch or 25mg/16hr patch, PLUS 4mg gum, OR 4mg lozenge</p>

Alfred Health	<p>High nicotine dependence (HSI score 5-6 or severe cravings with previous quit attempts) Nicotine patch 21mg/24 hours topically daily AND Nicotine 4 mg chewing gum: (1 piece of gum to be chewed as directed PRN up to every 1-2 hours, Maximum 10 pieces in 24 hours, (Avoid using >1 piece/ hr) OR Nicotine 4mg lozenges (1 lozenge to be used as directed PRN up to every 1-2hrs, Maximum 15 lozenges in 24hours) OR Nicotine 15mg inhalator (the contents of one cartridge to be inhaled PRN up to every 2-4 hrs, maximum of 6 cartridges in 24 hours) OR Nicotine 1mg mouth spray (Use 1-2 sprays PRN up to every 30-60 minutes, Maximum of 64 sprays in 24 hours Moderate nicotine dependence (HSI score 3-4 or significant cravings with previous quit attempts)</p> <p>Nicotine patch 21 mg/24 hours topically daily AND Nicotine 2 mg chewing gum: (1 piece of gum to be chewed as directed PRN up to every 1-2 hours, maximum 12 pieces in 24 hours, avoid using >1 piece/ hr) OR Nicotine 2mg lozenges (1 lozenge to be used as directed PRN up to every 1-2hrs, maximum 15 lozenges in 24hours) OR Nicotine 15mg inhalator (the contents of one cartridge to be inhaled PRN up to every 2-4 hrs, maximum of 6 cartridges in 24 hours) OR Nicotine 1mg mouth spray (Use 1-2 sprays PRN up to every 30-60 minutes, maximum of 64 sprays in 24 hours) Low nicotine dependence (HSI score 0-2 or mild cravings with previous quit attempts): Offer PRN intermittent formulations: Nicotine 2 mg chewing gum: (1 piece of gum to be chewed as directed PRN up to every 1-2 hours, maximum 12 pieces in 24 hours, avoid using >1 piece/ hr) OR Nicotine 2mg lozenges (1 lozenge to be used as directed PRN up to every 1-2 hrs, maximum15 lozenges in 24hours) OR Nicotine 15mg inhalator (the contents of one cartridge to be inhaled PRN up to every 2-4 hrs, maximum of 6 cartridges in 24 hours, OR Nicotine 1mg mouth spray (Use 1-2 sprays PRN up to every 30-60 minutes, maximum of 64 sprays in 24 hours)</p>
Quit for New life	<p>If patient is nicotine dependant (smokes > 10 CPD, or within 30 min of waking) then: 21mg/24 hr or 25mg/16 hr patch, PLUS</p>

	2mg/4mg lozenge OR 2mg/4mg gum OR 1mg spray OR 15mg inhalator Up to 12 weeks of therapy.
Therapeutic Guidelines	<p>Smokes > 10 CPD: 21mg/24 hr patch or 25mg/16 hr patch up to 12 weeks</p> <p>Smokes < 10 CPD: Patches usually not recommended. 15mg/24 hr patch or 10 mg/24hr patch up to 12 weeks</p> <p>Smokes > 20 CPD: 4mg gum</p> <p>Smokes < 20 CPD: 2mg gum</p> <p>1st cig < 30min of waking: 4mg lozenge</p> <p>1st cig > 30min of waking: 1.5mg/2mg lozenge</p> <p>For highly dependent people: 4mg Tablets</p> <p>For low-moderately dependant people: 2mg tablets</p> <p>For acute cravings: Oral spray</p>
Cancer Council Victoria	No specific guidance on dosing.
Department of Health and Ageing	<p>Patch</p> <p>>10 cigarettes per day and weight >45 kg 21 mg/24 h or 15 mg/16 h</p> <p><10 cigarettes per day or weight <45 kg or cardiovascular disease 14 mg/24 h or 10 mg/16 h</p>

	<p>Gum 10-20 cigarettes per day 2 mg (8-12 per day) >20 cigarettes per day 4 mg (6-10 per day)</p> <p>Inhaler >10 cigarettes per day 6-12 cartridges per day</p> <p>Lozenge First cigarette >30 minutes after waking 1.5 or 2 mg 1 lozenge every 1-2 h First cigarette <30 minutes after waking 4 mg (1 lozenge every 1-2 h)</p> <p>Sublingual tablet Low dependence (2 mg every 1-2 h) High dependence (two 2 mg every 1-2 h)</p>
The Women's	<p>HIS score 0 to 2 (low nicotine dependence): Quitline alone. If not controlled, add fast-acting NRT</p> <p>HIS score 3 to 4 (moderate nicotine dependence): Quitline ± fast-acting NRT (highest strength of fast-acting initially) If not controlled, add NRT patch</p> <p>HIS score 5 to 6 (high nicotine dependence): Quitline plus NRT patch ± fast-acting NRT If not controlled, maximise NRT patch and fast-acting dose</p>
ACT Health	<p>If patient smokes more than 10 cigarettes per day OR smokes their first cigarette within 60 minutes of waking OR has a history of withdrawal symptoms/cravings from quitting smoking, they are considered nicotine dependence and are offered NRT.</p> <p>Commence 1 x 21mg NRT patch every 24 hours (if smoking less than 14 CPD then 1 x 14mg patch) PLUS fast acting form of NRT (gum/lozenge/spray) every hour as needed</p>

	<p>If nicotine withdrawal or smoking persists increase dose either by: Adding a second patch to a total of 42mg/day OR One 21mg patch/day plus another 21mg/day patch for 12 hours during the day</p>
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Table 5: Summary of Behavioural Therapies Recommended by National Guidelines

Guideline	Recommended behavioural therapy
RACGP	Referral to telephone call-back counselling services should be offered to all people who smoke. (Strong recommendation, high certainty). In the absence of contraindications, pharmacotherapy (nicotine replacement therapy, varenicline or bupropion) is an effective aid when accompanied by behavioural support and should be recommended to all people who smoke who have evidence of nicotine dependence. Choice of pharmacotherapy is based on efficacy, clinical suitability and patient preference. (Strong recommendation, high certainty)
WA Health	Referral to Quitline, Local Cancer Council WA Fresh Start Program, Quitnow, Quit Coach, My Quit Buddy, GP or Pharmacist
Queensland Health	Not mentioned
NSW Health	Not mentioned
Alfred Health	<p>The following behavioural management strategies can be useful for coping with nicotine withdrawal symptoms and the behavioural and psychological connections associated with smoking:</p> <ul style="list-style-type: none"> • Practice the 4Ds; delay, deep breathe, drink water, and do something else. • Undertake relaxation and breathing exercises. • Exercise. • Focus on specific reasons to quit.
Quit for New Life	Not mentioned
Therapeutic Guidelines	Not mentioned
Cancer Council Victoria	<p>1-Individual counselling;</p> <ul style="list-style-type: none"> • Cognitive behavioural therapy. • Acceptance and commitment therapy. • Motivational interviewing. • Mindfulness. • Positive psychotherapy. <p>2- Group counselling. 3-Workplace 4-Peer support programs. 5-Residential treatments</p>
Department of Health and Ageing	Not mentioned
The Women's	<ul style="list-style-type: none"> • Refer to Quitline (via www.quit.org.au) to arrange for professional advice and for a free call-back service.
ACT Health	Referral to Quitline

1.4.1.5 Summary of national treatment algorithm

An explicit treatment algorithm or pathway was only included in the RACGP guidelines (see Figure 1, Appendix). Following a positive assessment for nicotine dependence and a patient's willingness to use pharmacotherapy, combination NRT or varenicline were considered the most effective pharmacotherapy. Bupropion was then considered for those who were not suitable for NRT or varenicline. Counselling was recommended in combination with pharmacotherapy.

This guidance was broadly consistent with most national guidelines included in this review which inferred that:

- NRT combination therapy was always preferred over monotherapy unless contraindicated or very low nicotine dependence
- Varenicline was considered more effective than NRT monotherapy and bupropion, and equivalent to NRT combination therapy
- NRT monotherapy and bupropion were considered equivalent.

Less consensus was found on the use of varenicline with NRT, with two guidelines (RACGP and Cancer Council Victoria) recommending the use of varenicline in combination with NRT for people who are attempting to quit smoking using varenicline alone accompanied by behavioural support, in contrast to the eTG which highlighted inconclusive benefits from this combination. Combining bupropion with either NRT or varenicline was generally not recommended because of inconclusive evidence for such combinations.

No guideline provided any guidance for patients who did not achieve abstinence including re-challenging with the same drug, sequencing of different treatment options, or timing between quit attempts. The only guidance included was the generic comment that when choosing a drug for a quit attempt, consideration should be given to experience with prior quit attempts.

1.4.1.6 Special Populations

NRT

Adolescents

NRT was explicitly considered appropriate for adolescents (12 years and over) only under clinical supervision across all guidelines, except for QLD, WA and QFNL where no specific recommendation was provided. The Cancer Council Victoria review stated that a randomised controlled trial found that NRT was not effective in promoting long-term abstinence among adolescents however they did note that it could be used in this population.

The use of NRT in patients 12 years of age or under was noted to be contraindicated as children were likely to be affected by nicotine and it could cause severe toxicity, which could be fatal (QFNL guidelines).

Cardiovascular Disease

The RACGP guidelines specifically recommended NRT for patients with stable cardiovascular disease, with caution recommended in patients with recent myocardial infarction, severe arrhythmias, unstable angina, or recent cerebrovascular events. This was also consistent with NSW health guidelines which recommended caution when using NRT in patients in hospital with acute cardiovascular events. The women's and ACT Health noted that there was no evidence of adverse events when NRT was used in patients with CVD. For all these guidelines, NRT use was recommended with medical supervision. WA Health simply noted that there were precautions for using NRT in patients with cardiovascular disease.

Pregnancy

NRT in pregnancy was explicitly considered in the QFNL and the Women's guidelines. QFNL and the Women's recommended NRT for pregnant women who were nicotine dependent, otherwise unable to quit, when the benefits of cessation outweighed the risks of NRT and the potential for smoking continued. In both guidelines NRT was recommended at any stage of the pregnancy (earlier the better) or in the postnatal period with preference for intermittent-use formulations for pregnant and breastfeeding women, reserving patches for when such formulations were not tolerated or if more NRT was required. RACGP, ACT Health and Alfred Health reiterated this guidance. WA Health simply noted that there were precautions for using NRT for pregnant and breastfeeding women.

Aboriginal & Torres Strait Islander

The Department of Health and Ageing was the only guideline that specifically and solely addressed smoking cessation amongst the broader Aboriginal and Torres Strait Islander population (rather than just pregnant women). As with non-Aboriginal and Torres Strait Islander populations, initiation and tailoring of pharmacotherapy were recommended according to level of nicotine dependence using the Fagerstrom test. NRT was recommended as monotherapy, and the use of combined NRT was recommended if abstinence could not be achieved with one NRT form alone, or if smokers still had cravings and withdrawal symptoms using only one form of NRT.

The RACGP guideline also mentioned Aboriginal and Torres Strait Islander populations however simply noted that little evidence has been generated in this population specifically and recommended use of smoking cessation interventions that have been shown effective generally.

Varenicline

The RACGP guidelines recommended the use of varenicline in those who smoke with mental health problems, however monitoring for unusual mood changes, depression, behaviour disturbance and suicidal thoughts was advised. The eTG and Department of Health and Ageing guidelines recommended the use of varenicline, with appropriate clinical oversight,

in people with schizophrenia and schizoaffective disorder, however the eTG noted limited evidence of safety and efficacy for varenicline in people with significant psychiatric illness.

In general, varenicline was not recommended for pregnant and breastfeeding women or for adolescents, and the eTG noted concerns about a possible small elevation in risk of cardiovascular events with the use of varenicline.

Bupropion

The RACGP and Department of Health and Ageing guidelines recommended against bupropion for women who were pregnant or breastfeeding.

NSW Health guidance and the eTG considered bupropion to be safe and effective for people with stable depression, cardiovascular and respiratory disease and in people with schizophrenia.

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1.4.2 International guidelines

Table 6 presents a summary of the key recommendations in the international guidelines included in this review.

1.4.2.1 Nicotine Replacement Therapy

All international guidelines recommended the use of NRT including long-acting products (patches) to provide a background level of coverage as well as a range of short-acting products (gum, lozenge, spray, inhalator) to manage acute cravings.

Dose forms, dose and treatment duration.

A range of products were available with some differences between jurisdictions. Generally, patches were available in a range of doses and were available as 16-hour patches (daytime use only) or 24-hour patches. A range of short-acting products were available, also in a range of doses.

Table 7 summarises the dosage recommendations for NRT within the included guidelines. Three guidelines (Canada, UK and NZ) provided specific recommendations around doses with treatment algorithms provided, whereas the US guideline simply referred prescribers to the product inserts of the individual products. The initial recommended strength of the patch, and the strength of the short-acting product, was dependant on the degree of nicotine dependence and was recommended to be individualised based on suggested treatment algorithms.

The NZ guideline specifically noted that underdosing was a known issue, with both Canadian and NZ guidelines suggesting that the use of higher dose NRT was more effective than lower dose (e.g., 4 mg gum versus 2 mg gum), especially in people who were more highly dependent.

The Canadian guidelines also noted that whilst high dose NRT patching (44/42 mg as multiple patches) had a very small or borderline additional benefit compared to the standard dose patching (22/21 mg) the higher strength was recommended for heavy smokers or for those who had not achieved abstinence with a lower strength patch. All guidelines recommended tailoring treatment to the patient's needs.

The Canadian guidelines recommended starting NRT anytime from the date of the quit attempt up to 4 weeks prior to the quit attempt (i.e. pre-loading), whilst the UK guidelines simply suggested that stopping smoking 'whilst using NRT' may reduce the chance of relapse.

The Canadian, NZ and UK guidelines all mentioned that NRT could be used as a component of a 'cut down to quit' strategy with the Canadian guidelines mentioning the use of gum to manage cravings whilst cutting the number of cigarettes smoked per day. The NZ and UK guidelines did not specify any particular NRT product or dose.

Canada, NZ and UK all recommended up to 12 weeks of NRT as a standard length of time for therapy however all recommended individual assessment and personalisation of the quitting regimen. Canada and the UK recommended tapering doses of patches over the 12

weeks (i.e. start with a higher patch strength, then slowly reduce). NZ noted there was no need for lower strength patches unless weaning was required. The UK and NZ guidelines recommended extending the period of use if the patient had not achieved abstinence. The US guideline did not provide guidance on length of treatment beyond referring healthcare providers to the prescribing information.

All guidelines recommended regular review of patients to assess progress of the quit attempt. If the patient was not responding at the interim review, the Canadian, NZ and UK guidelines recommended considering an increased dose (if using NRT) or trialling another therapy however no specific guidance was given around which therapy to try next.

Monotherapy versus combination therapy

All guidelines noted that combination therapy using a long-acting product (i.e. a patch) combined with a short-acting product (i.e. gum, lozenge, spray, inhalator) was more effective than NRT monotherapy.

The Canadian guideline specially recommended considering combinations of bupropion and varenicline (however noting limited safety data), varenicline and NRT, and bupropion and NRT. In contrast, the UK guidelines specifically recommended *against* the use of varenicline or bupropion combined with NRT and advised that varenicline and bupropion should not be prescribed together. The NZ guidelines did not comment on combining varenicline or bupropion with NRT.

With or without behavioural support

All guidelines noted that NRT combined with behavioural therapy was more effective than NRT alone.

Relapse prevention

The Canadian, NZ and US guidelines did not contain specific guidance on relapse prevention other than the NZ guideline suggesting that 'more NRT might be needed' at the end of a standard course. The UK guideline suggested tapering the NRT once a full course had been used.

Treatment failure/switching

Neither the US nor UK guidelines provided any specific guidance on the recommended treatment algorithm for people who failed to achieve abstinence with NRT or how to switch between treatments. The Canadian guidelines recommended the use of combination therapy of NRT and varenicline, or NRT and bupropion if only partial response was achieved with NRT as first line therapy.

The NZ clinical guidelines suggested that people who make repeated unsuccessful quit attempts were likely to be highly dependent smokers and may require more intensive support to succeed. The guidance document also indicated that evidence from randomised controlled trials suggested that people who had tried medication in the past could use bupropion and NRT together successfully. It was also suggested that treatment choice should be guided by learning from prior failures and by individual preference, and it was likely that a more intensive treatment would be required on a subsequent quit attempt.

No specific guidance was given around any suggested time-period between the use of NRT and different therapies for smoking cessation.

1.4.2.2 Varenicline

All guidelines recommended varenicline for use in smoking cessation and all recommended use in combination with behavioural support. The Canadian guidelines considered varenicline the most effective drug for smoking cessation with the UK guidelines considering varenicline and combination NRT to be equally most effective.

Dose forms, dose and treatment duration

Canadian, NZ and UK guidelines all recommend starting varenicline 7 - 14 days before quitting, the Canadian and UK guidelines then recommended using a lower dose for 3 days (0.5mg daily), a slightly higher dose for a further 4 days (0.5mg twice a day) before increasing to the full dose (1mg twice a day). The NZ guideline did not specify dosage, nor did the US guideline. The Canadian guideline recommended continuing for 12 to 24 weeks, NZ for 12 weeks, and the UK for 12 weeks with the option to extend if abstinence was achieved. All guidelines recommended regular review to assess progress.

Monotherapy versus combination therapy

The Canadian guideline recommended using varenicline in combination with NRT if only partial response was achieved with either when used as monotherapy. They also suggested combination of varenicline with bupropion if only partial response was achieved with monotherapy, however noted that safety information was lacking on this combination.

The UK guidelines did not recommend using varenicline with NRT and specifically stated that varenicline should not be prescribed with bupropion.

The NZ and US guidelines did not comment on combination therapy with varenicline.

With or without behavioural support

All guidelines recommended varenicline use in combination with behavioural support.

Relapse prevention

The Canadian, NZ and US guidelines did not contain specific mention of relapse prevention with use of varenicline. The UK guideline advised that a second 12-week course could be used to prevent relapse if abstinence was achieved at the end of the initial 12-week course.

Treatment failure/switching

The Canadian guidelines recommended trialling the combination of varenicline with NRT, or varenicline with bupropion (noting limited safety data) or switching to combination NRT if only partial response was achieved with varenicline monotherapy. No other international guideline provided guidance on a recommended treatment algorithm for people who failed varenicline treatment nor switching between varenicline and other treatments. The Canadian guidelines recommended trialling the combination of varenicline with NRT, or

varenicline with bupropion (noting limited safety data) or switching to combination NRT if only partial response was achieved with varenicline monotherapy.

No specific guidance was given about the recommended time-period between using varenicline and other therapies for smoking cessation.

1.4.2.3 Bupropion

All guidelines recommended bupropion, with the Canadian guideline noting it as effective as NRT (not specified whether NRT as monotherapy or combination NRT).

Dose forms, dose and treatment duration

All guidelines recommended starting 7 days before quitting and to continue for at least 7 weeks (NZ), 7 to 9 weeks (UK) and 7 to 12 weeks (Canada). The US guideline simply referred to the product insert for dosing. All guidelines recommended regular review to assess progress.

The Canadian and UK guidelines recommended starting with a lower dose (Canada: 150mg daily for 3 days, UK: 150mg daily for 6 days) then 150mg twice a day for 7 to 12 weeks (Canada) or 7 to 9 weeks (UK).

Monotherapy versus combination therapy

The US guidelines noted that NRT combined with bupropion may be more effective than each as monotherapy. The Canadian guideline suggested combination with either NRT or varenicline if only partial response (although noted that there is no safety evidence for varenicline and bupropion), and the UK guideline did not recommend combination with NRT, and specifically advised against combining with varenicline. The NZ guideline did not comment on combination therapy with bupropion.

With or without behavioural support

All guidelines recommended bupropion use in combination with behavioural therapy.

Relapse prevention

No guideline mentioned relapse prevention with the use of bupropion.

Treatment failure/switching

The Canadian guidelines recommended considering a combination of bupropion with NRT, or a combination of bupropion and varenicline (noting limited safety data) or switching to combination NRT if only partial response was achieved with bupropion monotherapy.

As per section 1.4.2.1, the NZ clinical guidelines indicated that evidence from randomised controlled trials indicated that people who had tried bupropion in the past could use bupropion and NRT together successfully.

No other international guideline provided any guidance on a recommended treatment algorithm for people who failed treatment with bupropion nor switching between treatments, except for the Canadian and NZ guidelines. The Canadian guidelines

recommended considering a combination of bupropion with NRT, or a combination of bupropion and varenicline (noting limited safety data) or switching to combination NRT if only partial response was achieved with bupropion monotherapy.

As per section 1.4.2.1, the NZ clinical guidelines indicated that there was evidence from randomised controlled trials that people who had tried medication in the past could use bupropion and NRT together successfully.

No specific guidance was given around the recommended time-period between the use bupropion and different therapies for smoking cessation.

1.4.2.4 Behavioural support – a closer look

All guidelines recommended use of behavioural support and noted that it should be offered to all patients regardless of whether they were also offered smoking cessation medication. All guidelines provided at least some detail about what techniques should be used and the frequency of intervention (Table 8). The NZ, Canadian and UK guidelines specifically recommended referral to local, trained stop smoking providers (e.g. Quitline). All guidelines recommended at least four sessions of therapy with the Canadian, UK and US guidelines noting that even 'very brief advice' of duration less than 3 minutes could improve the chances of smoking cessation. The Canadian and US guidelines included recommendations for in-person and telephone counselling as well as personalised print material. The UK guidelines recommended both in-person, one-on-one meetings, as well as group meetings, but did not discuss telephone counselling or print materials. The NZ guidelines did not discuss the mode of delivery.

The Canadian, US and NZ guidelines included specific recommended techniques to provide during counselling sessions (Table 8), whilst the UK guidelines referred to separate training materials. The Canadian, US and UK guidelines all included components of assessing smoking history, providing support during the quit attempt, information about what medications were available, as well as training in problem solving techniques.

The Canadian, US and NZ guidelines all advocated for a more tailored approach to behavioural support for specific populations including Aboriginal populations (Canada); Maori, Pacific Island, and mental health patients (NZ); and pregnant women (US).

Table 6: Summary of Key Recommendations – International Guidelines

Recommendation	CAN-ADAPT	U.S. Preventive Services Task Force	New Zealand guidelines	NICE stop smoking interventions and services
Overall				
Any treatment regime should be tailored to the patient	√	√	√	√
Pharmacotherapy combined with behavioural support is more effective than pharmacotherapy alone	√	√	√	√
Efficacy				
Combination of NRT patches with other short-acting forms of NRT is more effective than NRT monotherapy	√	√	√	√
Varenicline or combination NRT are most effective, followed by bupropion and NRT monotherapy	√	√	√	√
Dosing				
NRT should be prescribed for 12 weeks with the dose increased at review if needed	√		√	√
NRT dose should be tapered over time	√		Allowed but not required	√
NRT may be useful as part of a ‘cut down to quit’ attempt	√		√	√

Varenicline should be used for 12 weeks	√		√	√
Bupropion should be used for at least 7 weeks	√		√	√
Extension of treatment – treatment failure/relapse prevention				
Additional NRT should be prescribed if not abstinent at 12 weeks			√	√
If abstinence is not achieved with a standard course of bupropion it should be stopped				√
If abstinence is achieved with a standard course of varenicline, an additional course of 12 weeks could be prescribed to prevent relapse	√ (No specific requirement for abstinence at end of first course)			√
Special Populations				
NRT suitable for use in adolescents > 12 years	√		√	√
NRT (preferably short acting) preferred over continued smoking in pregnant women	√		√	√
NRT safe in Cardiovascular disease	√		√	√ (Caution advised for acutely unstable CVD)
Bupropion should not be used in patients with certain mental health issues	√			√

Table 7: Summary of NRT Dosing Recommendations – International Guidelines

Guideline	Dose Recommendation
CAN-ADAPTT (Canada)	<p style="text-align: center;">NRT Dosing</p> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p><10 CPD "Light" Smoker</p> <p>↓</p> <p>Start with:</p> <p>14mg patch x 1-4 weeks</p> </div> <div style="text-align: center;"> <p>10 - 29 CPD "Moderate" Smoker</p> <p>↓</p> <p>21mg patch x 1-4 weeks</p> </div> <div style="text-align: center;"> <p>30+ CPD "Heavy" Smoker</p> <p>↓</p> <p>28mg patch (21+7) x 1-4 weeks</p> </div> </div> <p style="text-align: center;">+ Choose one short-acting NRT (gum, lozenge, mouth spray or inhaler) for breakthrough cravings as needed</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">Follow up 1-4 weeks post quit date and assess smoking</p> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>If smoking 0 CPD</p> <p>Continue on current dose</p> </div> <div style="text-align: center;"> <p>If still smoking</p> <p>10+ CPD: Add a 21mg patch to current dose 6-9 CPD: Add a 14mg patch to current dose 1-5 CPD: Add a 7mg patch to current dose</p> <p>+ Choose one short-acting NRT for breakthrough cravings as needed</p> </div> </div>

<p>NZ guide to NRT prescribing</p>	<pre> graph TD A[Smokes after one hour of waking] --> B[Smokes fewer than 10 a day] A --> C[Smokes 10 or more a day] B --> D[2 mg gum or 1 mg lozenge or 14 mg patch] C --> E[21 mg patch with either 2 mg gum or 1 mg lozenge] F[Smokes within one hour of waking] --> G[Smokes fewer than 10 a day] F --> H[Smokes 10 or more a day] G --> I[21 mg patch with either 2 mg gum or 1 mg lozenge] H --> J[21 mg patch with either 4 mg gum or 2 mg lozenge] </pre>
<p>NICE (UK) – from BNF</p>	<p>Patches</p> <p>> 10 cigarettes daily apply a high-strength patch daily for 6–8 weeks, followed by the medium-strength patch for 2 weeks, and then the low-strength patch for the final 2 weeks;</p> <p>< 10 cigarettes daily start with the medium-strength patch for 6–8 weeks, followed by the low-strength patch for 2–4 weeks;</p> <p>if abstinence is not achieved, or if withdrawal symptoms are experienced, the strength of the patch used should be maintained or increased until the patient is stabilised; individuals using the high-strength patch who experience excessive side-effects, that do not resolve within a few days, should change to a medium-strength patch for the remainder of the initial period and then use the low-strength patch for 2–4 weeks.</p> <p>Short-acting NRT:</p> <p><20 CPD: 2mg gum OR 1 sublingual tablet OR 1mg lozenge as required</p> <p>>20 CPD OR requiring more than 15 pieces of 2mg gum OR failing to stop smoking with lower strength lozenges: 4mg gum OR 2mg lozenge as required.</p>

	OR other forms of NRT including inhaler or spray.
US	Refer to product inserts

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Table 8: Summary of Behavioural Therapies Recommended by International Guidelines

Guideline	Frequency/Number/Length of sessions	Mode of delivery	Recommended techniques
CANADA-ADAPTT	At least four	In person Telephone Tailored, print based materials	<ol style="list-style-type: none"> 1. Develop, build and maintain rapport. 2. Give information about your treatment programme (addressing both positive and realistic expectations). 3. Assess smoking history and past experience with stopping, including previous use of stop-smoking medicines. 4. Assess and strengthen commitment and ability to stop. 5. Enhance motivation and self-belief by affirming their decision and discussing ways to maintain their motivation. 6. Give information on stop-smoking medications. 7. Give information on tobacco withdrawal symptoms. 8. Help clients to develop a treatment plan and set a date to stop smoking (quit date). 9. Explain the importance of complete abstinence ('not a single puff') after their quit date. 10. Gain commitment to 'not a single puff'. 11. Use carbon monoxide monitors as a motivational tool. 12. Advise on gaining support from others. 13. Help with developing problem-solving and coping mechanisms for barriers, triggers and cues. 14. Advise on ways to change routines. 15. Advise on adjusting medication use. 16. Advise on staying smoke free and dealing with relapses.
U.S Preventive Services Task Force	At least four Dose-response relationship between the intensity of counselling and cessation rates (I.e. more or longer sessions improve cessation rates)	In person Telephone Tailored, print based materials	<p>Assessment of smoking status: Ask every patient about tobacco use Advise all tobacco users to quit Assess willingness of all tobacco users to make an attempt to quit Assist all tobacco users with their attempt to quit Arrange follow-up</p> <p>Effective counselling interventions provide social support and training in practical problem-solving skills. Training in problem-solving skills includes helping persons who smoke to recognize situations that increase their risk for smoking, develop coping skills to overcome common barriers to quitting, and develop a plan to quit</p>

	<p>Cessation rates may plateau after 90 min of counselling time.</p> <p>Both brief and longer sessions are effective in improving cessation rates.</p>		<p>Basic information about smoking and successful quitting should also be provided</p> <p>Complementary practices that improve cessation rates include motivational interviewing, assessing readiness to change, and offering more intensive counselling or referrals</p>
<p>New Zealand guidelines for helping people to stop smoking</p>	<p>At least four</p>	<p>Not specified</p>	<ul style="list-style-type: none"> • Develop, build and maintain rapport. • Give information about your treatment programme (addressing both positive and realistic expectations). • Assess smoking history and past experience with stopping, including previous use of stop-smoking medicines. • Assess and strengthen commitment and ability to stop. • Enhance motivation and self-belief by affirming their decision and discussing ways to maintain their motivation. • Give information on stop-smoking medicines. • Give information on tobacco withdrawal symptoms. • Help clients to develop a treatment plan and set a date to stop smoking (quit date). • Explain the importance of complete abstinence ('not a single puff') after their quit date. • Gain commitment to 'not a single puff'. • Use carbon monoxide monitors as a motivational tool. • Advise on gaining support from others. • Help with developing problem-solving and coping mechanisms for barriers, triggers and cues. • Advise on ways to change routines. • Advise on adjusting medication use. • Advise on staying smoke free and dealing with relapses.
<p>NICE stop smoking interventions and services</p>	<p>Weekly for at least 4 weeks</p>	<p>In person</p> <p>Group meetings</p>	<p>Brief Advice: Asking about current and past smoking behaviour, providing information on the consequences of smoking and stopping smoking, and advising on options for support and pharmacotherapy, in line with the NCSCT's training standard on very brief advice.</p> <p>Individual behavioural support involves scheduled face-to-face meetings between someone who smokes, and a counsellor trained in smoking cessation. Typically, it</p>

			<p>involves weekly sessions over a period of at least 4 weeks after the quit date and is normally combined with pharmacotherapy.</p> <p>Group behavioural support involves scheduled meetings in which people who smoke receive information, advice and encouragement and some form of behavioural intervention (for example, cognitive behavioural therapy). This therapy is offered weekly for at least the first 4 weeks of a quit attempt (that is, for 4 weeks after the quit date). It is normally combined with pharmacotherapy.</p>
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1.4.2.5 Summary of (inferred) international treatment algorithm

No guideline had a prescriptive treatment algorithm encompassing all pharmacotherapy options as all guidelines specifically prioritised tailoring of the pharmacotherapy to the patient. However, the following generalisations could be drawn:

- NRT combination therapy was always preferred over monotherapy unless contraindicated.
- Varenicline was considered more effective than NRT monotherapy and bupropion, and equivalent to NRT combination therapy (except in the UK guideline where varenicline was considered more efficacious than NRT combination therapy).
- NRT monotherapy and bupropion were considered roughly equivalent.

One guideline recommended combining NRT with varenicline or bupropion (Canada), and one guideline (UK) specifically recommended *against* combining these therapies. Although the Canadian guideline allowed for the combination of varenicline and bupropion, it was noted that safety data were not available for this combination. The NZ guideline noted some evidence for the combination of bupropion and NRT.

Follow-up between 1-4 weeks post quit date was recommended by the Canadian guidelines to determine if either full or partial response to treatment had been achieved. For those with partial response to the initial treatment, trialling another combination of therapies was recommended (see sections 1.4.1.2, 1.4.1.3 and 1.4.1.4). All other international guidelines recommended early follow-up but were not prescriptive in timing.

1.4.2.6 Special Populations

NRT

Two guidelines (NZ and UK) specifically recommended use of NRT in adolescents aged > 12 years. The Canadian guidelines referenced the NZ guidelines advice that NRT was recommended for use in adolescents >12 years of age, however, did not specifically recommend it themselves.

Two guidelines (Canada and NZ) specifically stated that NRT was safe to use in stable cardiovascular disease, while the UK guideline simply advised caution if a patient had acutely unstable cardiovascular disease.

For pregnant women, three guidelines (Canada, NZ and the UK) advised that use of NRT was preferred over continuing to smoke however non-pharmacological methods should ideally be used first. The Canadian and UK guidelines recommended using short-acting forms rather than patches if possible, and both NZ and the UK recommended removing patches before bed if they were being used. The US guidelines simply stated that the risk to benefit ratio of use of NRT in pregnancy was uncertain and therefore clinicians should take a shared decision-making approach.

Varenicline

All guidelines explicitly excluded the use of varenicline in pregnancy, or in adolescents less than 18 years of age. No other recommendations for the use of varenicline in other populations of interest were noted.

Bupropion

All guidelines did not recommend use in pregnancy, breastfeeding, or in adolescents less than 18 years of age. The UK guideline cautioned against use in patients with eating disorders, bipolar disorders, and acute benzodiazepine withdrawal. The Canadian guideline cautioned against use in anorexia and bulimia, and the NZ guideline simply recommended checking contraindications for the medication. The US guideline did not mention any other special populations other than pregnancy.

No other recommendations for the use of bupropion in populations of interest were noted.

1.4.3 Comparison of national and international clinical guidelines

Several similarities were apparent between the national and international guidelines.

- Approach to smoking cessation, including choice of pharmacotherapy, should be tailored to the patient.
- Varenicline was considered the most effective monotherapy, and at least equivalent to combination NRT.
- Combination NRT was considered more effective than monotherapy NRT or bupropion.
- All pharmacotherapy combined with behavioural support was considered more effective than pharmacotherapy alone.
- Referral to a specialised counselling service (e.g. Quitline or similar trained smoking cessation counsellors) was recommended.
- Using appropriate dosing for NRT, proportional to the level of nicotine dependence, was important, as was up-titrating the dose if there was limited response. Under-dosing was common and associated with risk of not achieving cessation.
- NRT should be used for 12 weeks, varenicline for 12 weeks and bupropion for at least 7 weeks. Some guidelines across both national and international jurisdictions allowed for a second course of NRT or varenicline, but not bupropion, to prevent relapse, or if complete abstinence was not achieved.
- Several guidelines allowed for double patching if the patient had very high nicotine dependence.
- No guidance was provided around length of time between sequential quit attempts
- NRT was considered appropriate for use in adolescents > 12 years, patients with stable CVD and pregnant women (although preference was given to achieving smoking cessation without the use of NRT in pregnant women).
- Bupropion should not be used in some patients with mental health issues.

There were some discrepancies between various guidelines, particularly around the use of combinations of NRT, varenicline and bupropion with some guidelines suggesting this was permissible in some or all combinations but others specifically recommending against these combinations.

Differences were also seen in how nicotine dependence was assessed, particularly in relation to NRT dosing. However, there was agreement on the overall principle that increased reliance on nicotine (whether measured by time to first cigarette, or number of cigarettes per day, or a combination of these) should trigger the use of higher doses of NRT at the time of quitting.

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1.5 RQ2: Comparison of PBS restrictions and TGA indications with Clinical guidelines

1.5.1 PBS Restrictions and TGA registrations

1.5.1.1 TGA Indication and dosing

There were 121 listings for nicotine containing products on the Australian Register of Therapeutic Goods (ARTG), including different dosage forms such as patch, gum, lozenge, mini lozenge, inhalator (buccal inhalation cartridge), mouth spray, and sublingual tablets as single therapy packs, as well as combination therapy packs containing both NRT patch and gum. There were also listings for varenicline (0.5 and 1 mg tablets) and bupropion (150 mg oral tablets). Table 15 shows the TGA indications for PBS-listed products for smoking cessation.

NRT

NRT was indicated for the treatment of nicotine dependence, and as an aid to smoking cessation for people over 12 years of age.

NRT patches were indicated for the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms thus facilitating smoking cessation in smokers motivated to quit.

NRT lozenges were indicated for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. Nicotine lozenges were also indicated as part of a smoking reduction strategy by smokers who were unable or not ready to stop smoking abruptly as a step towards stopping smoking. If possible, when stopping smoking, lozenges were recommended to be used in conjunction with a behavioural support program.

NRT chewing gums were indicated as an aid in the cessation of smoking in smokers with nicotine dependence. Chewing gums were also indicated as part of a smoking reduction strategy by smokers who were unable or not ready to stop smoking abruptly as a step towards stopping completely.

The consumer medicines information and product information for select NRT products were available via [NPS MedicineWise Medicine Finder](#)⁽²⁰⁾(see Table 16 for exemplars). The recommended starting doses of NRT patch and NRT gum were dependent on the level of nicotine dependence as determined by the number of cigarettes smoked per day and the presence of withdrawal symptoms or inability to cease smoking while using the lower strength product (gum only).

The doses of NRT patch and gum were gradually decreased over time. For NRT patches, dosing was stepped down at 3 to 4-week intervals over a 12-week period, with the transition through each stage and the duration of treatment dependent on the individual's response to treatment. Maintaining or increasing the dose was suggested if abstinence was not maintained or if withdrawal symptoms were experienced, and review of treatment should the duration of use exceed 9 months. One patch was recommended each day. Two

programs were approved: the first where the patch was started on the designated “quit day”. The second where the 21mg/24hour or 25mg/16-hour patch was used for two-weeks prior to quitting, followed by use of the nicotine patch in the usual way for the quit attempt⁽¹⁰⁾.

For NRT gum, the recommendation was to chew one piece of gum when urged to smoke. No more than 20 and 10 pieces of 2 mg and 4mg gum respectively per day was recommended with the usual daily dose expected to be 8 to 12 and 4 to 6 pieces of 2mg and 4mg gum respectively. Two programs were suggested. The first for people wishing to stop smoking at the commencement of the program, with gradual reduction in dose after the first 3 months of treatment, and cessation of gum within 6 months of treatment initiation. The second program was a cut-down-to-quit program, whereby gum was gradually increased while cigarettes were reduced to a level where smoking cessation was feasible. At that point, the first program was followed. In this program, if the number of cigarettes smoked per day had not reduced after 6 weeks, a review of treatment was recommended. A review of treatment was also generally recommended should the duration of use exceed 9 months, however regular use of the gum beyond 12 months was generally not recommended with QuitX Chewing Gum, although the need for longer treatment with gum to avoid a return to smoking for some ex-smokers was also acknowledged in the approved product information.

For NRT lozenges, a tapering dose over 12 weeks was also recommended, achieved by reducing the dosing frequency at weeks 7 and then again at week 10. People were instructed to take a lozenge when strongly tempted to smoke, and at least 9 lozenges per day were recommended during weeks 1-6. Only 1 lozenge was recommended at a time, with a maximum of 15 lozenges per day. Like NRT gum, a cut-down-to-quit program was also recommended, with the expectation of a review at 6 weeks if the number of cigarettes were not reduced or if a quit attempt after 6 months had not occurred. A review of treatment was also generally recommended should the duration of use exceed 9 months

NRT spray was also approved for use at the commencement of smoking cessation and in cut-down-to quit approaches⁽⁶⁾.

The same dosage recommendations for lozenges and gum were generally made for people aged 12-17 years, however the recommended treatment duration was only 12 weeks. Treatment durations longer than 12 weeks, but only up to 16 weeks, required a reassessment of the patients’ commitment to quit, maturity and the benefits of continued treatment. Moreover, counselling was considered paramount to the effectiveness of NRT in this age group. The pre-quit NRT patch regimen was not recommended for smokers in this age group.

In addition to monotherapy, the combination of NRT patch with short-acting dosage forms (e.g. chewing gum, lozenge, inhalator, QuickMist Mouth Spray) was an approved approach for people who were unable to quit smoking using NRT monotherapy, except for people aged 12-17 years. Using the Nicotinell brand as an exemplar, the highest strength NRT patch was used daily over 12 weeks with the lower strength gum used with cigarette cravings (daily dose: 4 to 12 pieces). After 12 weeks, doses were weaned by either stopping the patch and reducing the gum until no longer needed, or by reducing the strength of patch in 3 to 4-week intervals to zero followed by reducing the gum to zero.

The recommended dose for NRT from the Australian Medicines Handbook is provided below:

- **NRT patch:** For people with low-to-moderate nicotine dependence, the recommended dose was 14 mg/24 hours or 10–15 mg/16 hours, and to stop within 12 weeks. For people with moderate-to-high nicotine dependence, they can use 21 mg/24 hours or 15–25 mg/16 hours, and they can stop abruptly or by reducing strength of patches within 12 weeks.
- **Gum:** People with moderate nicotine dependence, the recommended dose was 8–12 pieces of 2 mg gum daily. While people with high nicotine dependence, 6–10 pieces of 4 mg gum daily should be used. After 4–8 weeks reduce to 2 mg, then stop or taper use over a further 4 weeks to zero.
- **Lozenge:** People with low-to-moderate nicotine dependence, a 1.5 mg or 2 mg lozenges should be used. People with moderate-to-high nicotine dependence should use 4 mg lozenges; for weeks 1 to 6, one lozenge every 1–2 hours was recommended, during weeks 7 to 9 one lozenge every 2–4 hours was recommended; weeks 10 to 12 one lozenge every 4–8 hours was recommended, and for weeks 12 to 24, one lozenge was recommended when there was a strong temptation to smoke.

VARENICLINE

Varenicline was indicated as an aid for smoking cessation in adults over the age of 18 years.

The recommended dose of varenicline was 1 mg twice daily following a 1-week titration as follows:

- Days 1 – 3: 0.5 mg once daily
- Days 4 – 7: 0.5 mg twice daily
- Day 8 – End of treatment: 1 mg twice daily

Dosing of varenicline was recommended to start 1 to 2 weeks before the designated quit date, or as an alternative regimen, varenicline could be started with a quit smoking date between days 8 and 35 of treatment. The recommended treatment length was 12 weeks, however for people who had successfully quit after the initial treatment course, an additional 12 weeks of treatment at 1mg twice daily was recommended to further increase the likelihood of long-term abstinence. In addition, for smokers who were not willing or able to quit abruptly, smoking could be reduced by 50% to zero over the first 12 weeks of therapy, and then an additional 12 weeks of treatment was recommended.

Additionally, further quit attempts were recommended for people who were motivated to quit but did not succeed in stopping during prior varenicline treatment, or who relapsed after treatment, once factors contributing to the failed attempt were identified and addressed.

BUPROPION

Bupropion tablets were indicated as a short-term adjunctive therapy for the treatment of nicotine dependence in those over the age of 18 years who were committed to quitting smoking, when used in conjunction with counselling for smoking cessation/abstinence.

The initial dose was 150 mg daily for three days, increasing to 150 mg twice daily. An interval of at least 8 hours between successive doses was recommended. The maximum single dose per day was 300 mg.

The recommended duration of treatment was at least 7 weeks, with discontinuation considered if significant progress towards abstinence had not been made by the seventh week of therapy, since it was unlikely that cessation would occur during that attempt.

1.5.1.2 PBS restrictions

NRT

NRT was indicated for people with nicotine dependence as a restricted benefit on the PBS general schedule and authority required benefit on the Repatriation Pharmaceutical Benefits schedule (RPBS).

Under the RPBS, only the 7, 14 and 21mg/24-hour strength patches (pack size 7) were available as an authority-required listing, with each prescription providing a maximum of 2 packs for all strengths (i.e. 14 patches) and no repeats for 7 and 14 mg/24-hour, while 2 repeats were allowed for 21 mg/24-hour strength patches. The clinical criteria for this listing were:

- *Patient must have indicated they are ready to cease smoking, AND*
- *Patient must have entered a comprehensive support and counselling program.*

There were no treatment criteria with this listing but the following note was observed:

- *Studies have shown that successful therapy with this drug is enhanced by patient participation in a support and counselling program.*

Under the general schedule, three dosage forms of NRT were listed as a restricted benefit without a population criterion: patch, lozenge and chewing gum. Available strengths of NRT patches were 7, 14, 21 mg/24 hours, and 25 mg/16 hours, with each prescription providing a maximum of 1 pack (28 patches) and 2 repeats. Two strengths of NRT gum and lozenges were available (2mg and 4 mg), providing 1 pack (216 pieces) with 2 repeats. The exception was the 2mg gum, which provided a maximum of 2 packs (432 pieces) and 1 repeat. No increase in the maximum quantity, number of units or number of repeats were allowed for any listing.

To access NRT under the general population restricted benefits, the clinical criteria for patients' eligibility were:

- *The treatment must be as an aid to achieving abstinence from smoking, AND*
- *The treatment must be the sole PBS-subsidised therapy for this condition, AND*
- *Patient must have indicated they are ready to cease smoking, AND*
- *Patient must not receive more than 12 weeks of PBS-subsidised nicotine replacement therapy per 12-month period.*

The PBS treatment criterion was: "Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated." Furthermore,

“details of the support and counselling program must be documented in the patient’s medical records at the time treatment is initiated.”

Within the general schedule listings for NRT patches (21 mg/ 24 hours and 25 mg/16 hours), lozenges (2 and 4 mg), and chewing gum (2 and 4 mg), there were also restricted benefits listed with an “Aboriginal or Torres Strait Islander” population criteria. These listings had the same item codes as the listings that did not have any population criteria (except for the Nicotinell Step 1, 21mg/24 hours listings which had separate item codes for each clinical criteria) , and thus had the same quantities and repeats. However, the following clinical criteria were observed:

- The treatment must be the sole PBS-subsidised therapy for this condition.

In addition, the following notes were observed:

- Only 2 courses of PBS-subsidised nicotine replacement therapy may be prescribed per 12-month period.
- Benefit is improved if used in conjunction with a comprehensive support and counselling program
- No increase in the maximum quantity, number of units or repeats may be authorised.

No PBS or RPBS listing covered two forms of NRT at once (i.e. no combination therapy).

The AMH dosing recommendations and assumptions used in PBS listing decisions and the assumed equi-effective doses are displayed in Table 9 and

Table 10 respectively:

Table 9: AMH Dosing Recommendations and Assumptions in PBS Listing

AMH Dosing Recommendations + Assumptions (NRT Gum, Lozenge and Patch)
High dependence
Gum: 8 pieces/day for 8 weeks followed by a halving of the dose (cutting gum strip in half) for the next 4 weeks Lozenge: Waking hours from 7am to 10pm (Total = 15 hours) 10 pieces/day for 6 weeks then 5 pieces/day for 3 weeks then 3 pieces/day for 3 weeks Patch: 1 patch/day for 12 weeks
Moderate dependence
Gum: 10 pieces/day for 12 weeks Lozenge: Waking hours from 7am to 10pm (Total = 15 hours) 10 pieces/day for 6 weeks then 5 pieces/day for 3 weeks then 3 pieces/day for 3 weeks Patch: 1 patch/day for 12 weeks

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Table 10: Accepted Equi-effective Doses of NRT

Form	Strength	Dose/12weeks
High dependence		
Gum	4mg	560
Lozenge	4mg	588
Patch	21mg	84
Moderate dependence		
Gum	2mg	840
Lozenge	2mg	588
Patch	14mg	84

G= gum, L=lozenge, P=patch

VARENICLINE

Varenicline was indicated for people with nicotine dependence under the PBS general schedule as an Authority Required (streamlined) restriction.

Two strengths were available; 500 microgram, and 1 mg, tablets. There were three different listings: commencement (500mg& 1mg, 11/42tabs, 0 repeats); continuation (1mg, 112 tabs, 0 repeats) and completion (1mg, 56 tabs, 2 repeats).

For the commencement phase, the clinical criteria were:

- *The treatment must be as an aid to achieving abstinence from smoking, AND*
- *The treatment must be the sole PBS-subsidised therapy for this condition, AND*
- *Patient must have indicated they are ready to cease smoking, AND*
- *Patient must not receive more than 24 weeks of PBS-subsidised treatment with this drug per 12-month period.*

The PBS treatment criteria for varenicline was “Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated.” Furthermore, details of the support and counselling program must be documented in the patient’s medical records at the time treatment was initiated, and clinical review was recommended within 2 to 3 weeks of the initial prescription being requested.

For the continuation phase, the clinical criteria were the same as for the commencement phase except that the patient did not need to (re)-indicate they were ready to cease smoking and instead the:

- *Patient must have previously received treatment with this drug during this current course of treatment.*

Furthermore, there were no clinical criteria explicitly restricting the duration of PBS subsidised treatment during this phase of treatment, nor was further documentation of the patient’s support and counselling program required in the treatment criteria.

For the completion phase, the clinical criteria were the same as the continuation phase with the following AND addition:

- *Patient must have ceased smoking in the process of completing an initial 12-weeks or ceased smoking following an initial 12-weeks of PBS-subsidised treatment with this drug in the course of treatment*

In addition, the following notes were observed for each listing:

- A course of treatment with this drug is 12 weeks or up to 24 weeks, if initial treatment of 12 weeks has been successful.
- The period between commencing varenicline and bupropion or a new course of varenicline must be at least 6 months (commencement phase only)
- A patient may only qualify for PBS-subsidised treatment under each treatment phases restriction once during a short-term course of treatment
- No increase in the maximum quantity, number of units or repeats may be authorised.

BUPROPION

Bupropion was indicated for people with nicotine dependence under the PBS general schedule as an Authority Required (streamlined) restriction.

Only one strength of bupropion, as a modified release tablet (150 mg) was available with two different pack sizes for commencement and completion respectively; (30 tabs, 0 repeats; 90 tabs, 0 repeats).

For the commencement treatment phase (i.e. short-term (9 weeks)), the clinical criteria were:

- *The treatment must be as an aid to achieving abstinence from smoking, AND*
- *The treatment must be the sole PBS-subsidised therapy for this condition, AND*
- *Patient must have indicated they are ready to cease smoking*
- *Patient must not receive more than 9 weeks of PBS-subsidised treatment with this drug per 12-month period.*

The PBS treatment criteria for bupropion was "Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program at the time PBS-subsidised treatment is initiated". Furthermore, details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated.

For the completion phase, the clinical criteria were the same as for the commencement phase, except that the patient was not required to indicate they were ready to cease smoking, and instead the:

- *Patient must have previously received PBS-subsidised treatment with this drug during this course of treatment*

The treatment criteria were also the same except that documentation of the support and counselling program in the patient's medical record was no longer required.

In addition, the following notes were observed:

- Clinical review is recommended within 2 to 3 weeks of the original prescription being requested.

- The period between commencing a course of bupropion hydrochloride and varenicline tartrate must be at least 6 months
- A patient may only qualify for PBS-subsidised treatment under this treatment phase restrictions once during a short-term course of treatment (commencement)
- No increase in the maximum quantity, number of units or repeats may be authorised.

A detailed list of PBS-listed medicines used for smoking cessation with TGA indications is provided in Table 15 in the appendix.

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1.5.2 Comparison of PBS Restrictions and TGA indications with the Clinical guidelines

1.5.2.1 Populations covered

Most of the national and international guidelines addressed the general population (all smokers) within the targeted setting. While specific populations were mentioned in many national and international guidelines (Table 18 and

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Table 19), the overall approach to pharmacotherapies for smoking cessation did not markedly differ aside from observing drug-specific precautions or contraindications. The only exceptions were in pregnancy and breastfeeding women, and adolescents. For pregnancy and breastfeeding there was consensus that pharmacotherapy should be avoided if possible, but if smoking cessation could not be achieved with behavioural support alone, then NRT was the preferred pharmacotherapy (specifically short-acting options if possible). For adolescents, there was general agreement that NRT could be used if needed. The Department of Health and Ageing, the Women's guidelines, and QFNL, were the only guideline that targeted an identified population, i.e. Aboriginal and Torres Strait Islanders, pregnancy populations in general, and antenatal and postnatal Aboriginal women, and women who identified as having an Aboriginal baby (and their cohabitants) who were participating in the Quit for New Life (QFNL) program respectively.

All PBS-approved indications for smoking cessation medicines were available to the general population. There were also specific listings for NRT in Aboriginal and Torres Strait Islander populations, but these did not include lower strength patches (i.e. 14mg & 7mg/24hours). There were no Aboriginal and Torres Strait Islander-specific listings for other smoking cessation therapies. There were no guidelines that recommended a different approach to the pharmacological treatment of smoking cessation for Aboriginal and Torres Strait Islander people nor against the use of other strengths of NRT patches, varenicline or bupropion.

All PBS-listed medicines for smoking cessation are for the treatment of nicotine dependence, however there were no requirements for documenting evidence of nicotine dependence or the level of dependence in the restrictions. In the national guidelines, most of the recommendations for the initiation of pharmacotherapy were based on evidence of nicotine dependence using measures such as the Fagerström test (see Table 12). Moreover, the level of nicotine dependence was consistently used in the guidelines to guide the initial dose of NRT.

PBS restrictions require pharmacotherapy (NRT, varenicline, and bupropion) to be used in conjunction with behavioural therapy or counselling but without specific guidance about the type or intensity of support. Guidelines also recommended conjunction of pharmacotherapy (NRT, varenicline, and bupropion) with behavioural support, with most guidelines simply recommending referral to a specialist provider such as Quitline, and some providing specific information around the type of behavioural support (see Table 5 and Table 8).

1.5.2.2 Dose/quantities/length of treatment

NRT

NRT (patches, gum, lozenges) were listed on the PBS as sole-subsidised therapy to aid quitting for people who participate in a support and counselling program. A maximum of 12 weeks of PBS-subsidised NRT was available per 12-month period under the general schedule for the general population, and up to two courses (of 12 weeks treatment) were available for Aboriginal and Torres Strait Islander people. There were no limits placed on the duration of NRT treatment (patches only) under the repatriation schedule.

Within the PBS restrictions, it was possible for people to access different strengths and forms of NRT, if only one strength or form was used at one time, and that the total PBS-supplied quantity in a year did not exceed the maximum allowable amount within each listing. Combination NRT and using NRT in conjunction with other pharmacotherapies for smoking cessation was therefore not allowed in the current PBS listing.

All national and international guidelines recommended the use of combination NRT for smoking cessation. While some guidelines (e.g. NSW health and NZ) indicated that for less nicotine dependent clients, the use of a patch or a single form of oral NRT may be sufficient to manage the urge to smoke and control withdrawal symptoms, there was consensus that combination NRT (i.e. patch and oral form) was more effective than monotherapy, especially for people with moderate to high nicotine dependence as well as people who were unable to remain abstinent or who continue to experience cravings and withdrawal symptoms using one type of NRT. This was also consistent with the TGA-approved approach to NRT treatment.

The recommended treatment length across guidelines was between 8 to 12 weeks which broadly aligned with the PBS restrictions within the general schedule (but not the Repatriation schedule which did not indicate a limit). However, RACGP, Alfred Health, Cancer Council Victoria, UK and NZ recommended that another course of therapy may be required in some patients: this was not available on the PBS restrictions for general population.

The quantity of patches supplied on the PBS aligned with the recommended doses in the guidelines, except for double-patching to achieve higher doses. The quantity of gum and lozenges supplied on the PBS roughly equated to 7 to 8 pieces per day. This was at the lower end of the maximum quantities outlined in the Alfred Health guidelines. Though lower than the maximum recommended doses in the NRT gum and lozenge Consumer Medicines Information (CMIs), this quantity was slightly less than the expected average of 8 to 12 pieces of 2mg gum and slightly above the expected average of 4 to 6 pieces of 4mg gum stated in the CMI and Product Information (PI).

Overall, the approved TGA dosing and length of treatment of NRT was consistent with clinical guidelines. However, cut-down-to quit and pre-quit use of NRT that are TGA-approved and are recommended strategies in the majority of national guidelines were not explicitly considered in the PBS restrictions, and may not be adequately accounted within the allowable quantities and repeats. Whether the current PBS restrictions preclude the use of NRT in this way is unclear.

VARENICLINE

Varenicline was available on the PBS as a short-term adjunctive therapy for nicotine dependence. It could be prescribed as a streamlined authority prescription for up to 24 weeks of continuous therapy for smoking cessation. Eligibility requirements included enrolling in a support and counselling program at the time of quitting, and abstinence at 12 weeks to access the second 12-week course of therapy. Unlike NRT there was no specific

listing for varenicline for Aboriginal and Torres Strait Islander populations despite there being no evidence in the guidelines to suggest that varenicline should not be used in these populations or that NRT was the preferred drug of choice. However, Aboriginal and Torres Strait Island people can access this medicine under the general restrictions.

The three PBS-listings for varenicline (initiation, continuation and completion), which includes a maximum of 24 weeks of therapy within a 12-month period, appeared to broadly align with the dosage regimen (dose titration) and lengths of treatment (12 to 24 weeks) recommended in the guidelines and the TGA indications. In line with the PBS restrictions, the TGA indication, the RACGP and Cancer Council Victoria and UK guidelines recommended the extended use of varenicline to prevent relapse in people who abstained in the process of completing or following an initial 12-weeks of therapy, however the RACGP expert advisory group rated the certainty of the evidence as low.

The TGA indications additionally suggested a repeat quit attempt in patients who did not successfully quit or who relapsed after treatment but were motivated to quit and had addressed the factors contributing to the failed attempt. Under the PBS restrictions, people who either did not successfully quit, or relapsed after successfully quitting would be required to wait 6 months between commencing varenicline and a new quit attempt with varenicline.

The combination of varenicline and other pharmacotherapies (NRT and bupropion) for smoking cessation was not allowed in the PBS listings, and this was consistent with most of guidelines. However, some guidelines recommended the use of varenicline in combination with NRT and bupropion for some people.

BUPROPION

Sustained-release bupropion was available on the PBS as a streamlined authority prescription for a short-term course of treatment (nine weeks) for nicotine dependence, with a comprehensive support and counselling program. Unlike NRT, there was no specific listing of bupropion for Aboriginal and Torres Strait Islander populations despite there being no evidence in the guidelines to suggest that bupropion should not be used in these populations nor that NRT was the preferred drug of choice in these populations. However, Aboriginal and Torres Strait Island people can access this medicine under the general restrictions.

The allowable quantities of bupropion within the PBS restrictions are consistent with the recommended dosing and length of treatment in the guidelines reviewed, however the TGA guidelines recommending cessation after 7 weeks of treatment if significant progress towards abstinence was not made by the seventh week. Within the PBS rules, a maximum of nine weeks of PBS-subsidised treatment with this drug was permitted per 12-month period.

Combination of bupropion and other pharmacotherapies (NRT and varenicline) for smoking cessation was not allowed in the current PBS listing. This was consistent with most national and international guidelines as most recommended bupropion as a monotherapy because

there was insufficient evidence to support combination of bupropion with either NRT or varenicline to improve rates of smoking cessation.

However, the Cancer Council Victoria guidelines highlighted evidence that concluded combination bupropion and varenicline may have greater efficacy in smoking cessation, which is consistent with the Canadian guidelines which allowed for such combination therapy (albeit noting a lack of safety data).

1.5.2.3 Lines of therapy/algorithm

The PBS restrictions for the general population are agnostic to line of therapy. All guidelines suggested that varenicline and combination NRT were the most effective treatment options, with NRT monotherapy and bupropion equivalent and less effective than varenicline and combination NRT. Despite this, all guidelines acknowledged that the choice of pharmacotherapy was highly individualised and based on patient preferences and clinical suitability.

Under the PBS restrictions for the general population, people who do not cease smoking following an initial course of treatment with NRT, varenicline or bupropion may not repeat another course of that same treatment in the same 12-month period but may access a different PBS-subsidised treatment for smoking cessation. However, the gap between bupropion and varenicline therapy must be 6 months. No guideline provided recommendations about subsequent treatment options should treatment on one agent fail. Similarly, neither the TGA nor the guidelines reviewed specified a 6-month or more gap in treatment between bupropion and varenicline treatment, including in the re-treatment of patients with varenicline who successfully quit following an initial 12-week course of varenicline.

NRT was the only pharmacotherapy for smoking cessation listed on the PBS for Aboriginal and Torres Strait Islander people, and, in addition to gum and lozenges, only the highest strength patch was listed. Without listing varenicline or bupropion in the same way, it could be inferred that NRT was the first-line choice of therapy for the Aboriginal and Torres Strait Islander people. This is not consistent with the national guidelines. Though NRT was the preferred treatment option for Aboriginal women who were pregnant or breastfeeding in the QFNL guidelines, intermittent forms of NRT were preferred. Access to all strengths of NRT patches, varenicline and bupropion is however possible for Aboriginal and Torres Strait Islander people under the general schedule as for people who do not identify as Aboriginal and Torres Strait Islander.

1.6 RQ3: Commonly used assessment measures used in guidelines to evaluate the severity of nicotine dependence

Nicotine dependence was considered under-recognised by clinicians (RACGP guidelines) and routine assessment of nicotine dependence was considered helpful in predicting whether a person who smokes was likely to experience nicotine withdrawal on stopping smoking, and the intensity and type of support that may be required to assist quitting.

All national guidelines recommended measurement of nicotine dependence and used the measured level of severity to guide the dose of NRT. For international guidelines, all except the US guidelines used a measure of nicotine dependency to guide NRT treatment.

To measure nicotine dependence, either the complete or a modified version of the self-reported Fagerström test for nicotine dependence (Table 12) was recommended. This instrument tests psychological and physiological dependence by asking the smoker a set of questions which are then scored and summed, with the total score of 6 or more indicating a high level of nicotine dependence.

Though the full Fagerström test for nicotine dependence was not routinely used in the guidelines, two questions from the Fagerström test were consistently used: time upon waking until the first cigarette is smoked, and the number of cigarettes per day (Table 11). Each of these questions were asked in the national guidelines. In contrast to the national guidelines, only the NZ guidelines asked both questions. The remaining guidelines (Canada, UK) solely relied on assessing the number of cigarettes smoked per day to guide NRT treatment. However, the RACGP guidelines indicated that time to first cigarette as the most reliable indicator of nicotine dependence as compared to the number of cigarettes per day, which is less reliable because of changed smoking habits from public health and clinical interventions and the fact that smokers tend to underestimate consumption levels.

Table 11: The Fagerström Test for Nicotine Dependence

No.	Question	Answer	Score
1	How soon after you wake up do you smoke your first cigarette?	Within 5 minutes	3
		6–30 minutes	2
		31–60 minutes	1
		After 60 minutes	0
2	Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes	1
		No	0
3	Which cigarette would you hate to give up most?	The first one in the morning	1
		All others	0
4	How many cigarettes per day do you smoke?	10 or less	0
		11-20	1
		21-30	2
		31 or more	3
5	Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
		No	0
6	Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
		No	0

Source: Heatherton T, Kozlowski L, Frecker R, and Fagerström K. The Fagerström test for nicotine dependence: A revision of the Fagerström tolerance questionnaire. *British Journal of Addiction*, 1991; 86(9):1119–27. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1932883>

Table 12: Modified Versions of Fagerström Used in Clinical Guidelines

Guideline	Question/s asked	Response criteria	Interpretation
National			
RACGP	How many minutes until the first cigarette after waking?	Open-ended	Nicotine dependence if: Smoking within 30 minutes 10 or more per day
	How many cigarettes a day do you smoke?	Open-ended	

	Cravings or withdrawal symptoms in previous quit attempts	Yes/No	Previous cravings/withdrawals
QLD Health	How many cigarettes do you smoke in a typical day? Is this more than 10 cigarettes?	Open & Yes/No	Nicotine dependence if: Yes to one or more questions
	Do you smoke your first cigarette within 60 minutes of waking?	Yes/No	
	Do you have a history of withdrawal symptoms/cravings from quitting smoking?	Yes/No	
NSW Health	How soon after waking do you have your first cigarette?	Open	Nicotine dependence if: Smoking within 30minutes More than 10 cigarettes a day History of withdrawal symptoms
	How many cigarettes do you smoke each day?	Open	
	If you have previously attempted to quit, did you experience withdrawals or cravings?	Yes/No	
QFNL	How soon after waking do you have your first cigarette?	Open	Nicotine dependence if: Smoking within 30 minutes More than 10 cigarettes per day Unable to quit if: Repeated unsuccessful quit attempts Unable to quit for 2 weeks
	How many cigarettes do you smoke per day	Open	
	How many unsuccessful quit attempts in the past 12 months	Open	
	Have you been able to quit for 2 weeks?	Yes/No	
Alfred Health	How soon after you wake up do you smoke your first cigarette?	As per Fagerström	Responses to question 1-4 are summed and a score of: High dependence: 5-6 Moderate dependence: 3-4 Low dependence: 0-2 If the patient has experienced severe cravings when previously not smoking, consider commencing NRT at higher dosages
	Do you find it difficult to stop smoking in no-smoking areas?	As per Fagerström	
	Which cigarette would you hate to give up most?	As per Fagerström	
	How many cigarettes per day do you smoke?	As per Fagerström	
	Have you previously experienced severe cravings when not smoking?	Yes/No	
eTG	How many cigarettes a day do you smoke per day?	Open	

	How soon after waking up do you smoke your first cigarette?	Open	<p>High dependence: waking at night to smoke or smoking within the first 5 minutes; 30 or more cigarettes a day</p> <p>Moderate dependence: smoking within 30 minutes after waking; 20-30 cigarettes per day</p> <p>Low-to-moderate: not smoking within 30 minutes after waking; 10-20 cigarettes per day</p> <p>Low dependence: not smoking in first hour after waking; fewer than 10 cigarettes per day</p>
The Women's	The Heaviness Smoking Index (HSI): 1- How many cigarettes do you smoke each day?	As per Fagerström	<p>As per Fagerström:</p> <p>10 or fewer: score (0)</p> <p>11 to 20: score (1)</p> <p>21 to 30: score (2)</p> <p>31 or more: score (3)</p>
	2- How soon after waking do you smoke your first cigarette?	As per Fagerström	<p>As per Fagerström:</p> <p>After 60 minutes: score (0)</p> <p>31 to 60 minutes: score (1)</p> <p>6 to 30 minutes: score (2)</p> <p>Within 5 minutes: score (3)</p>
ACT Health	How many cigarettes do you smoke in a typical day?	Open-ended	If answer to first question is greater than 10, or Yes to either of the other questions, considered nicotine dependent.
	Do you smoke your first cigarette within 60 min of waking?	Yes/No	
	Do you have a history of withdrawal symptoms/cravings from quitting smoking?	Yes/No	
International			
Canada	How many cigarettes do you smoke per day?	Open-ended	<p>Heavy smoker: 30+ cigarettes per day</p> <p>Moderate smoker: 10-29 cigarettes per day</p> <p>Light smoker: <10 cigarettes per day</p>
New Zealand	How soon after waking up do you smoke your first cigarette?	Open ended	Low level: smokes <10 cigarettes a day and after 1 hour of waking

	How many cigarettes do you smoke per day?	Open ended	Medium: smoke <10 cigarettes and day but within 1 hour of waking OR smokes >10 cigarettes a day and after 1 hour of waking High: smokes >10 cigarettes a day and within 1 hour of waking
United Kingdom	How many cigarettes do you smoke per day?	Open ended	High: >10-20 cigarettes per day

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1.7 RQ4: Misalignment between TGA-approved indications, PBS restrictions and clinical guidelines for smoking cessation pharmacotherapies

General

- Measuring the level of nicotine dependence was considered necessary in determining a patient's eligibility for pharmacotherapy (NRT, varenicline, and bupropion) and the subsequent dosing of NRT across most of the national and international guidelines using different measures of nicotine dependence such as the Fagerström test, or various subsets of such questions. Under the PBS restrictions, while all pharmacotherapies were indicated for the treatment of nicotine dependence, there were no criteria for NRT dosing based on the level of nicotine dependence. NRT was the only pharmacotherapy for smoking cessation that had a specific PBS-listing for Aboriginal and Torres Strait Islander populations despite there being no evidence to suggest that NRT was the preferred drug of choice in these populations. However, Aboriginal and Torres Strait Island people can access other medicines under the general PBS restrictions.

Specific to NRT

- While all national and international guidelines recommended the use of combination NRT for smoking cessation, stating that combination NRT (i.e. patch and oral form) was more effective than monotherapy, the current PBS restrictions would not allow for the use of combination therapy.
- RACGP guidelines recommended an additional course of NRT beyond the initial 12-week period to prevent relapse events, while this was not available under the PBS restrictions for the general population.
- Cut-down to quit and pre-quit use of NRT was TGA-approved and recommended in the majority of national and some international guidelines. However, under the PBS restrictions, this was not explicitly considered and may not be adequately accounted for within the allowable quantities and repeats. Whether the current PBS restrictions preclude the use of NRT in this way is unclear.
- 'Double-patching' was specifically recommended by several guidelines, in the context of high nicotine dependence, or patients still experiencing cravings despite maximal dosing. Current PBS restrictions would not allow for this under the allowable quantities and repeats.
- TGA guidance and several international guidelines recommend titrating the dose of the patch and 'weaning' the patient off the patches, however this was not consistent with the national guidelines.
- While the PBS listing exclusively allows for 2 courses (24-weeks) of NRT for Aboriginal and Torres Strait Islander populations per 12-month period, there were no recommendations made by clinical guidelines that specifically favour use of an additional course of NRT (beyond the standard course) among these populations over and above recommendations for the general population.

Specific to varenicline

- The PBS listing allows for an additional 12-week course in people who have abstained from smoking after an initial 12-week course (i.e. relapse prevention). An extended course of varenicline treatment for those who abstained from smoking was considered of low certainty evidence in the RACGP guidelines but was approved in the TGA indication. The Cancer Council Victoria, and some international guidelines also recommended an additional 12 weeks of therapy for people who have not successfully quit after the first 12 weeks of treatment.
- Most national and international guidelines recommended the use of varenicline as monotherapy, however two national guidelines (RACGP and Cancer Council Victoria) and one international guideline (Canada) recommended the use of varenicline in combination with NRT as an alternative to varenicline alone. The current PBS prescribing criteria do not allow prescription of more than one PBS-subsidised therapy for smoking cessation at a time.
- Varenicline was considered the most effective monotherapy, however, unlike NRT, there was no restricted benefit for varenicline with a population criteria for Aboriginal and Torres Strait Islander populations.
- The PBS listing required a maximum of 24 weeks of varenicline therapy in every 12-month period and that the period between commencing a course of varenicline and a new course of varenicline (i.e varenicline re-treatment) or bupropion must be at least 6 months. The TGA indication suggested re-treatment with varenicline may be appropriate but did not specify a required waiting period between subsequent courses. Moreover, no national or international guideline provided recommendations about varenicline re-treatment nor the required waiting period subsequent to varenicline or bupropion treatment prior to commencing another course of the same, or a different treatment.

Specific to bupropion

- One international guideline (Canada) specified that that combination bupropion and varenicline appeared to have greater efficacy in smoking cessation than varenicline alone. This is inconsistent with the PBS prescribing criteria which only allowed prescription of one therapy at a time but was supported by the Cancer Council Victoria guidance
- The PBS listing required that the period between commencing a course of bupropion hydrochloride and varenicline tartrate must be at least 6 months. No national nor international guideline provided any recommendation around a waiting period when switching between these two medicines.

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Appendix

Table 13: Quality Assessment of the National Guidelines

Domain	RACGP	WA Health	Queensland Health	NSW Ministry Health	Cancer Council Victoria	Alfred Health-Updated	Quit for New Life	Therapeutic Guidelines	Department of Health and Ageing	The Women's	ACT Health
Domain 1. Scope and Purpose	100	100	100	100	100	88.9	100	100	100	100	100
Domain 2. Stakeholder Involvement	100	55.6	33.3	50	100	83.3	88.3	88.9	83.3	83.3	66.7
Domain 3. Rigour of Development	87.5	18.8	6.3	39.6	64.6	0	35.4	31.3	25	25	35.4
Domain 4. Clarity of Presentation	100	100	100	100	100	88.9	100	100	100	100	100
Domain 5. Applicability	50	50	37.5	100	87.5	16.7	25	25	29.2	54.2	83.3
Domain 6. Editorial Independence	100	50	0	0	50	50	0	50	50	50	50
Overall AGREE II score	7	5	4	6	7	5	5	6	6	6	6

Table 14: Quality Assessment of the International Guidelines

Domain	CAN-ADAPTT	U.S. Preventive Services Task Force	New Zealand	NICE
Domain 1. Scope and Purpose	100	100	100	100
Domain 2. Stakeholder Involvement	83.3	83.3	83.3	100
Domain 3. Rigour of Development	100	54.2	87.5	100
Domain 4. Clarity of Presentation	100	100	100	100
Domain 5. Applicability	25	25	100	87.5
Domain 6. Editorial Independence	50	0	75	91.7
Overall AGREE II score	6	6	7	7

Table 15: TGA Registrations for PBS-listed Pharmacotherapies for Smoking Cessation

Medicine	Brand/Sponsor	TGA indication
Nicotine 21mg/24hr patch	Nicotinell Step 1 (28) - Orion Laboratories Pty Ltd	Treatment of nicotine dependence, as an aid to smoking cessation. The Nicotinell Step 1 patch may also be used by people who smoke 20 or more cigarettes per day for two weeks prior to quitting smoking.
	Nicabate CQ 21 (7) - GlaxoSmithKline Australia Pty Ltd	For the treatment of nicotine dependence as an aid to smoking cessation.
	Nicabate P (28) - GlaxoSmithKline Australia Pty Ltd	For the treatment of nicotine dependence as an aid to smoking cessation. Nicabate P patches may also be used by people who smoke 15 or more cigarettes per day for two weeks prior to quitting smoking.
	Quit X (7) - Alphapharm Pty Ltd	Treatment of nicotine dependence, as an aid to smoking cessation.
Nicotine 14mg/24hr patch	Quit X (7) - Alphapharm Pty Ltd	Treatment of nicotine dependence, as an aid to smoking cessation.
	Nicabate CQ 14 (7) - GlaxoSmithKline Australia Pty Ltd	For the treatment of nicotine dependence as an aid to smoking cessation.
	Nicotinell Step 2 (28) - Orion Laboratories Pty Ltd	Treatment of nicotine dependence, as an aid to smoking cessation.
Nicotine 7mg/24hr patch	Quit X (7) - Alphapharm Pty Ltd	Treatment of nicotine dependence, as an aid to smoking cessation.
	Nicotinell Step 3 (28) - Orion Laboratories Pty Ltd	Treatment of nicotine dependence, as an aid to smoking cessation.

Nicotine 25mg/16hr patch	Nicorette 16hr Invisipatch (28) - Johnson & Johnson Pacific Pty Limited	For the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms thus facilitating smoking cessation in smokers motivated to quit. For smokers who are currently unable or not ready to stop smoking immediately, the Nicorette 25 mg/16 hour Invisipatch can also be used for two weeks by people who smoke 15 or more cigarettes per day in a preparation phase to reduce the need to smoke prior to stopping smoking immediately.
Nicotine Gum 2mg	Nicotinell coated chewing gum 2mg (tropical fruit, ice mint, classic and mint flavours) - Orion Laboratories Pty Ltd	An aid in the cessation of smoking in smokers with nicotine dependence. Nicotinell Coated Chewing Gums may also be used as part of a smoking education strategy by smokers who are unable or not ready to stop smoking abruptly as a step towards stopping completely.
Nicotine Gum 4mg	Nicotinell coated chewing gum 4mg (tropical fruit, ice mint, classic and mint flavours) - Orion Laboratories Pty Ltd	An aid in the cessation of smoking in smokers with nicotine dependence. Nicotinell Coated Chewing Gums may also be used as part of a smoking reduction strategy by smokers who are unable or not ready to stop smoking abruptly as a step towards stopping completely.
Nicotine Lozenge 2mg	Nicotinell peppermint lozenge 2mg blister pack - Orion Laboratories Pty Ltd	Relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. Nicotine Lozenges may also be used as part of a smoking reduction strategy by smokers who are unable or not ready to stop smoking abruptly as a step towards stopping smoking. If possible, when stopping smoking, should be used in conjunction with behavioural support program.
Nicotine Lozenge 4mg	Nicotinell peppermint lozenge 4mg blister pack - Orion Laboratories Pty Ltd	Relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. Nicotine Lozenges may also be used as part of a smoking reduction strategy by smokers who are unable or not ready to stop smoking abruptly as a step towards stopping smoking. If possible, when stopping smoking, should be used in conjunction with behavioural support program.
Bupropion	Zyban 150mg sustained release tablet blister pack - Aspen Pharmacare Australia Pty Limited	Zyban SR tablets are indicated as a short-term adjunctive therapy for the treatment of nicotine dependence in those who are committed to quitting smoking, when used in conjunction with counselling for smoking cessation/abstinence. (Effective 11 April 2019). Note: There is a broader indication listed for Zyban on the ARTG for other products with a slightly different presentation (& listed as export only) - effective 21/6/16 and 25/5/12. The sponsor for these alternative listings is GSK (GSK is not a sponsor for the PBS Zyban listing)

		“For the treatment of nicotine dependence as an aid to smoking cessation”
Varenicline	Champix 0.5mg and 1.0mg blister pack - Pfizer Australia Pty Ltd	Champix is indicated as an aid for smoking cessation in adults over the age of 18 years
	Champix 1.0mg blister pack - Pfizer Australia Pty Ltd	Champix is indicated as an aid for smoking cessation in adults over the age of 18 years
	Generic Brands 0.5 and 1mg pack, 1mg pack (not PBS listed) - Terrywhite chemists - APO - APOTEX - Chemmart - Blooms the chemist	Varenicline tablets are indicated as an aid to smoking cessation in adults over the age of 18 years. (same for all generic brands)

Table 16: NPS Medicine Wise – Product Information / Consumer Medicines information

Nicotine Patches	Nicotine Gum	Nicotine Lozenge
<p>Program A: If you smoked more than 20 cigarettes each day</p> <p>Weeks 1 - 4: 1. Stop cigarette smoking and use one Nicotinell Step 1 patch each day for 3 to 4 weeks. 2. After 3 to 4 weeks you should no longer be smoking cigarettes and can move on to Nicotinell Step 2. However if you are still smoking, consult your doctor or pharmacist.</p> <p>Weeks 5 - 8: 1. Use one Nicotinell Step 2 patch each day for another 3 to 4 weeks. 2. After week 3, if you are still a non-smoker, you can move on to Nicotinell Step 3. But if you have smoked during weeks 5 – 8, consult your doctor or pharmacist.</p> <p>Weeks 9 - 12: 1. Use one Nicotinell Step 3 patch each day for another 3 to 4 weeks. 2. After week 9 to 12 you should stop using the patches. You have become a non-smoker. Congratulations!</p> <p>Program B: If you smoked less than 20 cigarettes each day</p> <p>Weeks 1 - 4:</p>	<p>At the beginning of the “quit day”, start to use Nicotinell Chewing Gum before any cigarettes have been smoked.</p> <p>The appropriate dose will depend on your previous smoking habits.</p> <p>Use 2 mg gum if: <input type="checkbox"/> you were smoking less than 20 cigarettes a day</p> <p>If, while using the 2 mg gum, your withdrawal symptoms remain so strong as to threaten relapse, then you should use the 4 mg gum.</p> <p>Use 4 mg gum if: <input type="checkbox"/> you were smoking more than 20 cigarettes a day <input type="checkbox"/> you have previously failed to stop smoking with 2 mg gum</p> <p>Chew one piece of gum when you feel the urge to smoke.</p> <p>Do not use more than 20 pieces of the 2 mg gum or 10 pieces of the 4 mg gum in a day. Most people use 8-12 pieces of the 2mg gum or 4-6 pieces of the 4mg gum in a day.</p> <p>Usage Program for adults</p> <p>There are two usage programs you can follow:</p>	<p>Dosage</p> <p>For adults (and young people aged over 12 years) who want to stop in a few months, Nicotinell® Lozenges should be used according to the following schedule:</p> <p>Weeks 1 to 6: 1 lozenge every 1 to 2 hours</p> <p>Weeks 7 to 9: 1 lozenge every 2 to 4 hours</p> <p>Weeks 10 to 12: 1 lozenge every 4 to 8 hours</p> <p>To help you stay smoke free over the next 12 weeks, take 1 lozenge in situations where you are strongly tempted to smoke.</p> <p>During the initial treatment period (weeks 1 to 6) adults aged 18 years and over should use at least nine lozenges per day.</p> <p>Do not use more than 1 lozenge at a time and do not use more than 15 lozenges per day.</p> <p>For adult smokers who want to stop over several months: Use a lozenge whenever you have a strong urge to smoke instead of smoking a cigarette. When you have reduced the number of cigarettes you smoke each day to a level from which you feel you can quit completely then use the schedule in the section above for smokers who want to quit in a few months. See your</p>

<p>1. Stop cigarette smoking and use one Nicotinell Step 2 patch each day for 3 to 4 weeks.</p> <p>2. After 3 to 4 weeks you should no longer be smoking cigarettes and can move on to Nicotinell Step 3. But if you are still smoking consult your doctor or pharmacist.</p> <p>Weeks 5 - 12:</p> <p>1. Use one Nicotinell Step 3 patch each day for 5 to 8 weeks.</p> <p>2. If you have smoked during your course of treatment in weeks 5 – 8, please consult your doctor or pharmacist before proceeding further.</p> <p>3. Similarly, if you have smoked during your course of treatment in weeks 9 – 12, please consult your doctor or pharmacist.</p> <p>4. After week 9 to 12 you should stop using the patches. You have become a non-smoker. Congratulations!</p>	<p>Program A. If you would like to stop smoking completely before starting the program:</p> <ul style="list-style-type: none"> ☑ After about 3 months, gradually cut down the amount of gum you chew each day. ☑ When you are down to 1-2 pieces a day, you can stop using Nicotinell Gum. ☑ You should be able to stop completely within 6 months from the start of the treatment. <p>Program B. If you cannot stop smoking completely before starting the program:</p> <ul style="list-style-type: none"> ☑ Gradually increase gum use, while cutting down smoking. ☑ When you have cut down the number of cigarettes you smoke to a level you feel you can quit completely, follow Program A. ☑ If you have not cut down the number of cigarettes you smoke each day after 6 weeks, see your doctor or pharmacist. <p>Combination therapy</p> <p>If you have relapsed in the past or if you experience cravings while using a single form of nicotine replacement therapy (NRT), you can combine the use of Nicotinell patch with Nicotinell chewing gum 2 mg.</p> <p>The combination is more effective than either product alone in people who have been unable to quit smoking using a single NRT method, increasing your chances of successfully quitting.</p> <p>When using Nicotinell Step 1 patch, chew one piece of Nicotinell chewing gum 2 mg if you get a craving. Use at least 4 pieces of gum and not more than 12 pieces in a day. Continue for 12 weeks.</p>	<p>pharmacist or doctor if you have not reduced the number of cigarettes you smoke each day after 6 weeks, or if you have not begun an attempt to quit completely after 6 months.</p> <p>Children 12 to 17 years old – same as above except “do not use for longer than 12 weeks.”</p>
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	<p>After 12 weeks, you can wean yourself off therapy by either of the following methods:</p> <ol style="list-style-type: none">1. Stop use of Nicotinell patch and gradually reduce the number of Nicotinell chewing gum 2 mg you use until you no longer need them.2.a. Use Nicotinell Step 2 patch for 3-4 weeks, while using the same number of pieces of Nicotinell chewing gum 2 mg in a day that you have routinely used.b. Then use Nicotinell Step 3 for a further 3-4 weeks, while using the same number of pieces of Nicotinell chewing gum 2 mg in a day that you have routinely used.c. When patch use is no longer needed, gradually reduce the number of gums you use until you no longer need them. <p>Children 12 to 17 years old – same as above except “do not use for longer than 12 weeks.”</p>	
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Table 17: Summary of PBS Restrictions for NRT, Varenicline, and Bupropion

PBS restrictions	NRT patches, gum, lozenge	Varenicline	Bupropion
Indication	Nicotine dependence	Nicotine dependence	Nicotine dependence
Clinical criteria	<p>The treatment must be as an aid to achieving abstinence from smoking,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>Patient must have indicated they are ready to cease smoking,</p> <p>AND</p> <p>Patient must not receive more than 12 weeks of PBS-subsidised nicotine replacement therapy per 12-month period.</p>	<p>The treatment must be as an aid to achieving abstinence from smoking,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>Patient must have indicated they are ready to cease smoking,</p> <p>AND</p> <p>Patient must not receive more than 24 weeks of PBS-subsidised treatment with this drug per 12-month period.</p>	<p>The treatment must be as an aid to achieving abstinence from smoking,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>Patient must have previously received PBS-subsidised treatment with this drug during this current course of treatment,</p> <p>AND</p> <p>Patient must not receive more than 9 weeks of PBS-subsidised treatment with this drug per 12-month period.</p>
Treatment criteria	Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated.	Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated.	Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated.
Population criteria	For Aboriginal or a Torres Strait Islanders: (lozenge, chewing gum, patch)	N/A	N/A

	<ul style="list-style-type: none"> The treatment must be the sole PBS-subsidised therapy for this condition. Only 2 courses of PBS-subsidised nicotine replacement therapy may be prescribed per 12-month period. 		
Treatment phase	Commencement of a short-term (12 weeks) course of treatment	Commencement, continuation, completion of a short-term (12 weeks or 24 weeks) course of treatment	Commencement, completion of a short-term (9 weeks) course of treatment
Strength, Maximum quantity and repeats	PATCH: 7mg, 14mg, 21mg, 25mg; 28patches; 2 repeats GUM: 2mg, 432 pieces, 1 repeat GUM: 4mg; 216 pieces; 2 repeats LOZENGE: 2mg; 216 pieces; 2 repeats LOZENGE: 4mg; 216 pieces; 2 repeats	500mg/1mg; 11/42 tablets; 0 repeats (commencement) 1mg, 112 tabs; 0 repeats (continuation) 1 mg, 56 tablets; 2 repeats (completion)	150mg; 30 tabs; 0 repeats (commencement) 150mg; 90 tabs; 0 repeats (completion)

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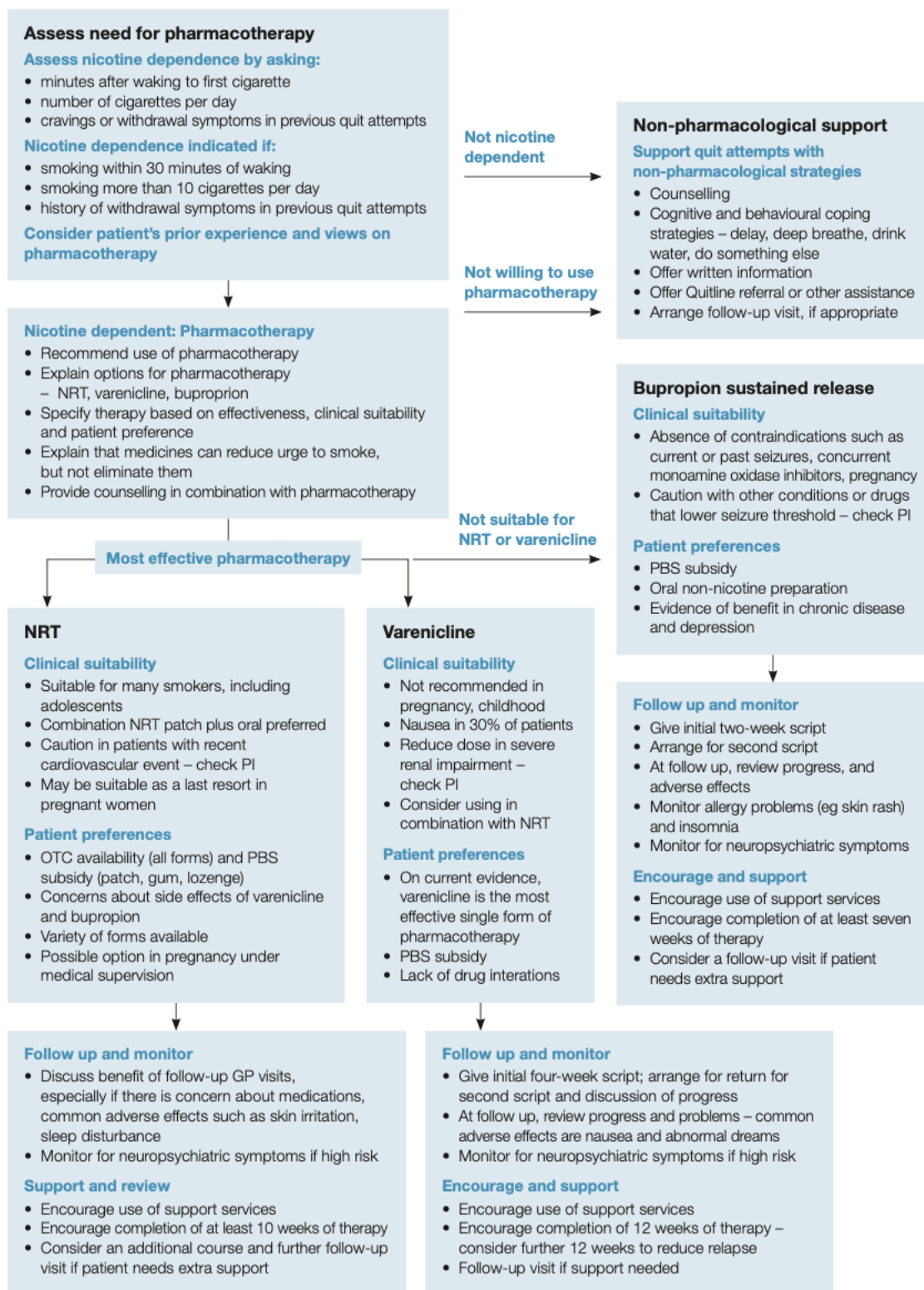


Figure 1: Treatment Algorithm, RACGP Guidelines

Source: RACGP guidelines, Figure 2.2. GP, general practitioner, OTC, over the counter, PBS, pharmaceutical Benefits Scheme, PI product information

Table 18: Populations Identified by National Guidelines

Guideline	General population	Specific population covered
RACGP	Yes	Pregnant women, cardiovascular disease, Breastfeeding, People with mental illness, Women, People who smoke and drink heavily, Aboriginal and Torres Strait Islander, CALD, Adolescents, and other young people.
QLD	Yes	All smokers, Any local precautions/protocols (e.g. microvascular surgery, skin grafts etc.), Children <12 years of age, Pregnant/lactating, Recent cardiovascular event <48 hours, Under Clozapine
WA	Yes	Pregnant or breastfeeding women, patients with cardiovascular disease, diabetics, Mental health co-morbidity, Patients with a Fagerström Test score 5+, Aboriginal patients, Culturally and Linguistically Diverse (CALD) patients, Parents or guardians of paediatric patients.
NSW	Yes	Pregnancy and lactation, young people, Aboriginal people, People in NSW correctional facilities, People with a mental illness, People with other drug dependence issues, People from culturally and linguistically diverse backgrounds
VIC	Yes	Adolescents, Cardiovascular, Pregnancy and breast feeding
QFNL	No	Antenatal and postnatal Aboriginal women and women who identify as having an Aboriginal baby (and their cohabitants) who are participating in the Quit for new life (QFNL) program.
eTG	Yes	Pregnancy, adolescents, patients with CVD.
Alfred Health	Yes	Not mentioned
Department of Health and Ageing	No	Aboriginal and Torres Strait Islander people including kids over 12 years old, people with heart problems, people with kidney problems, people who need to have NRT for a long time (over 6 months), pregnant women, and people who smoke cannabis.
The Women's	No	Pregnancy including mental illness, cardiovascular disease, diabetes mellitus or gestational diabetes mellitus, generalised skin disease, nausea and vomiting, phenylketonuria (PKU), dentures or complicated dental work, and asthma.

Table 19: Populations Identified by International Guidelines

Guideline	General Population	Specific Population
CAN-ADAPTT	Yes	First nations people, in-hospital patients, Youth > 12 years, Mentally ill patients,
NICE (UK)	Yes	Pregnant or breastfeeding women, youth > 12 years.
NZ	Yes	Pregnant or breastfeeding women, youth > 12 years, patients with stable cardiovascular disease
USPTF	Yes	Pregnant or breastfeeding women.

Table 20: Summary table of PBS restrictions versus main guidelines (general population)

Criteria	PBS restriction	RACGP
NRT (patch, lozenge, and gum)		
Assessment of nicotine dependence	Not required	Fagerstrom test
Strength	N/A	<p>According to level of nicotine dependence</p> <p>Use all below for up to 12 months, but limited evidence for effectiveness longer than 24 weeks.</p> <p>Smokes > 30 min from waking and <10 CPD: 2mg or 1.5mg lozenge, OR 2mg gum, OR 1 mg spray, OR 15mg inhaler</p> <p>Smokes > 30 min from waking and > 10 CPD: 21mg/24 hr patch, PLUS 2mg gum, OR 2mg/1.5mg lozenge, OR 1 mg spray, OR 15mg inhaler</p> <p>Smokes < 30 min from waking and <10 CPD 21mg/24hr patch, PLUS 2mg gum, OR 2mg/1.5mg lozenge, OR 1mg spray, OR 15mg inhaler</p> <p>Smokes < 30 min from waking and > 10 CPD 21mg/24h patch, PLUS 4mg gum, OR 4mg lozenge, OR 1mg spray, OR 15mg inhalator</p>
Duration of treatment	12 weeks	8-12 weeks

Quit date/pre-loading	Not allowed	2 weeks (higher strength NRT patches)
Cut down to quit	Not allowed	Within 6 months
Relapse prevention	Not allowed	Additional 12 weeks course
Behavioural therapy	Required (mandatory)	Highly recommended
Combination therapy	Not allowed	Recommended for those who are nicotine dependent
Varenicline		
Assessment of nicotine dependence	Not required	Fagerstrom test
Strength	N/A PBS subsidised strengths:	Days 1–3: 0.5 mg once per day Days 4–7: 0.5 mg twice per day Day 8: 1 mg twice per day
Duration of treatment	12 weeks	12 weeks
Quit date/pre-loading	Not allowed	Fixed approach: 1-2 weeks Flexible approach: between days 8 and 35 of treatment
Relapse prevention	Additional 12 weeks course	Additional 12 weeks course
Cut down to quit	Not allowed	Not recommended
Behavioural therapy	Required (mandatory)	Highly recommended
Combination therapy	Not allowed	Recommended with NRT
Period between commencing a course of varenicline and bupropion	6 months	No recommendation
Bupropion		
Assessment of nicotine dependence	Not required	Fagerstrom test
Strength	N/A (PBS subsidised strength: 150 mg)	150 mg once per day for the first 3 days and then 150 mg twice per day until the end of the course.
Duration of treatment	9 weeks	7-9 weeks
Quit date/pre-loading	Not allowed	1 week before
Relapse prevention	Not allowed	Not recommended
Cut down to quit	Not allowed	Not recommended

Behavioural therapy	Required (mandatory)	Highly recommended
Combination therapy	Not allowed	Not recommended
Period between commencing a course of bupropion and varenicline	6 months	No recommendation

Table 21: Summary table of PBS restrictions versus main guidelines (Aboriginal and Torres Strait Islander population)

Criteria	PBS restriction	Department of Health and Ageing
NRT (patch, lozenge, and gum)		
Assessment of nicotine dependence	Not required	Fagerstrom test
Strength	N/A Higher strength patch	According to level of nicotine dependence
Duration of treatment	12 weeks	8-12 weeks
Relapse prevention	Allowed (Additional 12-week course)	Additional 12-week course
Quit date/pre-loading	Insufficient quantities allowed to be prescribed	Higher strength NRT patches (21 mg/24 hrs) for 2 weeks
Cut down to quit	Insufficient quantities allowed to be prescribed	Within 6 months
Behavioural therapy	Recommended but not mandatory	Highly recommended
Combination therapy	Not allowed	Recommended for those who are either experiencing cravings or unable to quit using one form of NRT