SUBMISSION

POST-MARKET REVIEW OF SMOKING CESSATION TREATMENTS

TERMS OF REFERENCE 1-3

Submitted: May 2020

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EXECUTIVE SUMMARY

Pfizer is the applicant for the smoking cessation treatment, varenicline, therefore this submission to the Terms of Reference focuses largely on varenicline.

Term of reference 1: Collate the current clinical guidelines for medicines for smoking cessation and compare these to the Therapeutic Goods Administration (TGA) and PBS restrictions for these medicines

A literature search identified eighteen guidelines including the most recently revised Royal Australian College of General Practitioners (RACGP) guide for healthcare professionals supporting smoking cessation (second edition) released in late 2019.

The RACGP guide recommends providing brief advice to quit smoking, behavioural support and a choice of pharmacotherapy, which includes varenicline, nicotine replacement therapy (NRT) and bupropion (noting that bupropion is less effective than varenicline and NRT, and combination NRT is more effective than NRT monotherapy), based on efficacy, clinical suitability and patient preference. For individuals who are attempting to quit smoking using varenicline accompanied by behavioural support, the guide indicates that clinicians might recommend varenicline in combination with NRT.

Similar to the RACGP guide, most guidelines use a structured approach and stress the benefit of a combination of behavioural therapy or counselling together with pharmacotherapy. Pharmacotherapy is either outlined without making specific recommendations as to which option to prescribe or they recommend specific lines of therapy. Where lines of therapy are recommended, first line options are predominantly varenicline, NRT or NRT combination therapy. In some guidelines, bupropion is not included or included as a second- or third-line option. This is in recognition of its lower efficacy and greater side-effects, relative to other treatments.

Like the RACGP guide, the latest guidelines also include NRT in combination with varenicline as a treatment option. Some guidelines also include combinations with bupropion as treatment options. Other therapies in guidelines include nortriptyline and clonidine, both of which are not registered for smoking cessation in Australia. Nortriptyline is indicated for the treatment of depression, while clonidine is indicated for hypertension, vascular headaches, migraine and menopausal-associated vasodilation symptoms. In addition, cytisine is not currently available in Australia as a registered therapeutic product outside of the clinical trial setting (note, available as a complementary medicine in the form of cytisus laburnum extract).

Varenicline, bupropion and NRT are registered for smoking cessation in Australia and available on the Pharmaceutical Benefits Scheme (PBS). The PBS restrictions require patients to be committed to stopping smoking and be enrolled in a counselling program, with the exception of Aboriginal and Torres Strait Islanders, for which NRT reimbursement does not require that smokers are enrolled in such a program but notes that benefit of NRT is improved with a counselling program. The restrictions stipulate a maximum period of treatment per year of 9 weeks for bupropion, 12 weeks for NRT and 24 weeks for varenicline if patients who have ceased smoking after 12 weeks are prescribed the additional 12 week course to increase the chance of long-term success, alternatively the treatment period is 12 weeks. In addition, the restriction also stipulates that there must be a period of 6 months between commencing a course of bupropion

and varenicline and between two courses of varenicline. Finally, the PBS-listings stipulate that bupropion, NRT and varenicline are to be used as sole PBS-subsidised treatments, whereas the guidelines recommend combination NRT, and many include combination varenicline and NRT and bupropion and NRT in some cases.

Term of Reference 2: Review the utilisation of PBS-listed medicines for smoking cessation including but not limited to patient demographics, time on treatment, and the proportion using PBS subsidised combination treatment.

The majority of usage of varenicline is in individuals who are 35-49 years and 50-64 years old. Of individuals initiating varenicline 55% were male and 56% of all varenicline scripts were for males.

Only 11% of individuals initiating varenicline had recently received PBS-reimbursed NRT and 4% of individuals who had been initiated on varenicline received NRT soon afterwards. These analyses could be assumed to indicate combination use. However, it is important to note that NRT may be purchased privately without a prescription and used with varenicline, thereafter, combination use may be significantly higher. In addition, PBS data do not capture patient-specific usage of smoking cessation therapies for Aboriginal people and Torres Strait Islanders under the Section 100 Remote Area Aboriginal Health Service measure. As indicated in the submission by NACCHO and supported by Pfizer, this population has considerably higher smoking rates and a demonstrated need for enhanced access to combination therapy including varenicline + NRT. Existing usage of this varenicline + NRT combination therapy is not currently captured in the statistics.

Term of reference 3: Review the efficacy and safety of nicotine replacement therapy, varenicline and bupropion for smoking cessation including combination therapies not currently PBS subsidized

Varenicline has been extremely well studied in both pivotal randomised clinical studies conducted for registration approval as well as in extensive post-marketing studies to demonstrate ongoing effectiveness and alleviate safety concerns. In addition, clinical studies have been performed in special populations who would benefit from smoking cessation. The addition of NRT to varenicline has also been studied.

Monotherapy

Pivotal clinical evidence

Efficacy

Four direct randomised trials (Anthenelli *et al*, 2016; Aubin *et al*, 2008; Gonzales *et al*, 2006; Jorenby *et al*, 2006) provide evidence of the comparative benefit of varenicline versus placebo and active comparators as an aid to smoking cessation.

In Anthenelli *et al* (2016), varenicline was superior to bupropion, NRT patch and placebo at the end of treatment (weeks 9–12) and follow-up (weeks 9–24). Bupropion was similar in efficacy to NRT patch and bupropion and NRT patch were superior to placebo. Odds ratios for the overall cohort (Weeks 9 to 12) were as follows: varenicline vs placebo: 3.61 (3.07 to 4.24); varenicline vs NRT patch: 1.68 (1.46 to 1.93); varenicline vs bupropion: 1.75 (1.52 to 2.01); bupropion vs

placebo: 2.07 (1.75 to 2.45); and NRT patch vs placebo: 2.15 (1.82 to 2.54). Odds ratios (Weeks 9 to 24) were as follows: varenicline vs placebo: 2.74 (2.28 to 3.30); varenicline vs NRT patch: 1.52 (1.29 to 1.78); varenicline vs bupropion: 1.45 (1.24 to 1.70); bupropion vs placebo: 1.89 (1.56 to 2.29); and NRT patch vs placebo: 1.81 (1.49 to 2.19).

The primary outcome in both Gonzales *et al*, 2006 and Jorenby *et al*, 2006 trials was a 4-week continuous quit rate (CQR) from week 9 to 12. In both Gonzales *et al*, 2006 and Jorenby *et al*, 2006, smokers who were randomised to receive varenicline achieved highly statistically significant superior cessation rates compared to smokers randomised to bupropion or placebo. A pooled analysis of the trial results for 4-week CQR Weeks 9 to 12 reported a relative risk (RR) of 1.5 (95% CI: 1.3, 1.7, p<0.00001).

The secondary outcome measure in both Gonzales *et al*, 2006 and Jorenby *et al*, 2006 was continuous abstinence (CA) from week 9 to 52. The pooled analysis showed that smokers who received varenicline were statistically significantly more likely to have remained abstinent from smoking from Week 9 to Week 52 than smokers who received bupropion with a RR of 1.4 (95% CI: 1.1, 1.8, p=0.002).

In the Aubin *et al*, 2008 trial, the primary and secondary outcomes referred to continuous abstinence rate (CA) in the last 4 weeks of treatment. The secondary outcome was measured for the last 4 weeks of treatment through week 52 (NRT: weeks 8-52; varenicline: weeks 9-52). Review of the results showed a higher response rate in smokers who received varenicline than in patients who received NRT in the last 4 weeks of treatment, i.e. between week 9 and week 12 (varenicline: 55.9% versus NRT: 43.2%; OR 1.70, 95% CI: 1.26-2.28). At week 52, the response rate in the varenicline group was higher than in the NRT group, i.e. 26.1% vs. 20.3% respectively (OR: 1.40, 95% CI: 0.99-1.99, p=0.056) but the difference was not statistically significant. Results mentioned above are from the primary analysis population. When analysis is performed on all randomised patients, the results are very similar but the difference at 52 weeks was statistically significant (varenicline: 25.9%; NRT: 19.8%; OR 1.44, 95% CI 1.02-2.03, p=0.040).

Safety

One of the main objectives of Anthenelli *et al*, 2016 was to compare neuropsychiatric adverse events between smoking cessation treatments in patients with and without prespecified psychiatric diagnoses. In the non-psychiatric cohort, 1.3% participants in the varenicline group reported moderate and severe neuropsychiatric adverse events compared to 2.2% in the bupropion group, 2.5% in the nicotine patch group, and 2.4% in the placebo group. In the psychiatric cohort, moderate and severe neuropsychiatric adverse events were reported in 6.5% of participants in the varenicline group, 6.7% in the bupropion group, 5.2% in the nicotine patch group, and 4.9% in the placebo group.

Across cohorts, the most frequent adverse events by treatment group were nausea (varenicline, 25% [511 of 2016 participants]), insomnia (bupropion, 12% [245 of 2006 participants]), abnormal dreams (nicotine patch, 12% [251 of 2022 participants]), and headache (placebo, 10% [199 of 2014 participants]).

Adverse events in the other three head to head RCTs (Gonzales *et al*, 2006, Jorenby *et al*, 2006 and Aubin *et al*, 2008) were similar to Anthenelli *et al* (2016). Varenicline's most frequently reported adverse events (AEs) in the other three head to head RCTs (Gonzales *et al*, 2006, Jorenby *et al*, 2006 and Aubin *et al*, 2008) were nausea, insomnia, abnormal dreams and headache. Safety results from the three trials showed that varenicline, when compared to bupropion, placebo or NRT, is associated with a higher rate of abnormal dreams, headache and nausea. As it relates to insomnia, varenicline is associated with a lower rate than bupropion and a slightly higher rate than placebo and NRT.

Other clinical studies

Forty-six publications were identified which included forty studies. Of the forty studies: twenty six were randomised controlled trials (RCTs) and three were open-label studies. Twenty four of the RCTs were placebo-controlled. Of the remaining two, one compared 12-weeks of varenicline + 12 weeks of placebo to twenty-four weeks of varenicline and one compared varenicline to NRT. Other study designs include: a prospective comparative study and prospective and retrospective cohort studies. Studies were comparative (vs bupropion and NRT) and non-comparative.

Populations included alcohol-dependent smokers; asthmatic smokers; smokers with stable cardiovascular disease; Asian smokers; smokers attending GP practice; smokers living with HIV; smokers with cancer; smokers with COPD; smokers with neurodevelopmental disorders; smokers with mental health disorders; hospitalised patients; smokers scheduled for surgery; smokers enrolled in smoking cessation programs; young adult smokers and light smokers.

Studies were also conducted allowing flexible quit dates; in individuals not willing to quit within the next month but willing to reduce cigarette consumption and make a quit attempt at 3 months; comparing 12 weeks of varenicline to placebo in individuals who had quit after an additional 12 weeks of treatment; and employing a 6-week preloading regime with varenicline.

The majority of comparative studies demonstrated superiority of varenicline to comparators for 7-day point prevalence of abstinence and continuous abstinence, and non-comparative studies showed favourable outcomes with varenicline.

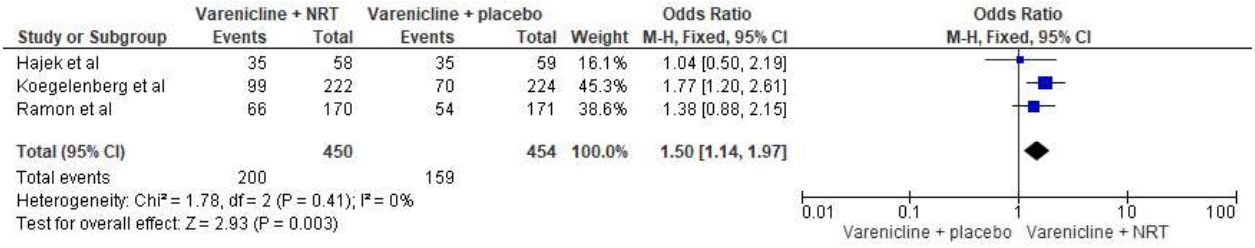
The adverse event profile was similar to that found in the pivotal clinical evidence. The most common adverse events were nausea, headache, insomnia and vivid dreams. The studies also confirm the findings from the EAGLES study and add to the evidence of the acceptability of varenicline for the treatment of individuals with mental health conditions.

Combination therapy

Three RCTs (Hajek *et al*, 2013; Koegelenberg *et al*, 2014 and Ramon *et al*, 2014) and two observational studies (Berg *et al*, 2007; Ebbert *et al*, 2009) considered varenicline in combination with NRT.

Of the three combination RCTs, only Koegelenberg *et al* (2014) showed a significant beneficial effect for the combination of varenicline + NRT. This is likely to be due to the treatment regimen used where NRT was initiated one week prior to varenicline and two weeks prior to the Target

Quit Date (TQD), whereas Hajek *et al* (2013) and Ramon *et al* 2014 both used NRT one week post-varenicline/from the TQD. In Ramon *et al* (2014), the differences were significant in individuals who smoked >29 cigarettes per day. The forest plot (OR) for the three studies is shown below and shows an overall combined beneficial effect.



The observational studies showed the benefit of the combination of varenicline + NRT, although these were small observational/cohort analyses.

The adverse event profile of the combination is similar to that of individual agents, however the RCTs reported a numerically greater incidence of nausea, insomnia abnormal dreams, sleep disturbance, skin reactions, constipation, headache and depression with combination therapy versus varenicline monotherapy.

Despite the less than favourable results in Hajek *et al* (2013) and in individuals who smoked ≤29 cigarettes in Ramon *et al* (2014), the evidence suggests that combination therapy could be considered in individuals who have not been successful with varenicline monotherapy and in certain risk groups.

Pfizer is supportive of the National Aboriginal Community Controlled Health Organisation's (NACCHO's) submission to this review requesting consideration of combination therapy, including varenicline + NRT, in Aboriginal and Torres Strait Islander smokers.

Subject to the findings of Terms of Reference 1, 2 and 3, review the cost-effectiveness of medicines for smoking cessation.

Economic evaluations in Pharmaceutical Benefits Advisory Committee (PBAC) submissions for varenicline have consistently shown this smoking cessation agent to be highly cost-effective.

The first major PBAC submission for varenicline was to obtain PBS-listing for initiation and continuation of varenicline and compared varenicline to bupropion, which was Pharmaceutical Benefits Scheme (PBS)-listed for smoking cessation at the time.

The second major PBAC submission for varenicline was for a second 12 weeks of treatment in individuals who had ceased smoking after the initial 12 weeks of treatment. The economic evaluation in this submission compared varenicline to placebo in individuals who had ceased smoking after 12 weeks of treatment.

A third major PBAC submission and a resubmission were to propose that a second course of varenicline be permitted 6 months after the initial course of treatment, instead of being required

to wait until the next year. This submission compared varenicline to a combination of placebo, bupropion and NRT in individuals who had previously received a course of varenicline.

The economic evaluations from these PBAC submissions were updated by including the most recent:

- Australian population statistics,
- Australian age-specific death rates,
- Australian smoking rates, and
- PBS costs (2020) for varenicline, bupropion and NRT.

In addition, economic evaluations were performed with the efficacy estimates adjusted to reflect the usage of the smoking cessation treatments in clinical practice i.e. the efficacy estimates were reduced due to discontinuation of treatment and consequent reduction in overall efficacy in these patients. In addition costs were reduced based on usage of smoking cessation agents in clinical practice Finally, estimates for current smoking-related deaths were included.

Further economic evaluations, which had not been included in the original submissions, were performed:

- Varenicline vs NRT, and
- Varenicline + NRT vs NRT.

The updates to previous economic analyses as well as these addition economic analyses show that varenicline remains highly cost-effective in all scenarios. Whether performed using the total treatment costs and evidence from clinical studies or adapted to reflect discontinuation rates seen in clinical practice, varenicline is highly cost-effective with a cost per QALY of <$15,000 for all evaluations except the unadjusted evaluation of a second course of varenicline in individuals who quit after 12 weeks of treatment. In this case the cost per QALY was <$20,000.

Further details of the cost-effectiveness analysis are provided as a separate confidential document.

Conclusion of submission to post-market review of smoking cessation treatments

This submission provides evidence that varenicline is extremely effective for smoking cessation as demonstrated in clinical studies performed for registration many studies performed in a large number of populations since registration. Due to concerns in individuals with mental health issues a number of studies have been performed in these populations and have alleviated these concerns.

Varenicline is used as is outlined in international guidelines and the RACGP guide. These guidelines also recommend the use of varenicline in combination with NRT and this should be considered in individuals who do not achieve smoking cessation on monotherapy.

Finally varenicline continues to be a highly cost-effective treatment both using results of clinical studies and with discontinuation rates seen in clinical practice.

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

1.1 Clinical guidelines

A literature search was performed to identify clinical guidelines on the management of smoking cessation including use of smoking cessation treatments. Non-English guidelines were excluded. The Royal Australian College of General Practitioners (RACGP) guide for health professionals supporting smoking cessation is the most recent and of most relevance in Australia; detailed recommendations from the second edition released in late 2019 are provided below. Seventeen other guidelines were identified and are compared with each other and the RACGP guide.

1.1.1. RACGP guide

The recommendations of the guide are as follows:

The role of health professionals

- **Recommendation 1** – All people who smoke should be offered brief advice to quit smoking.
- **Recommendation 2** – A system for identifying all people who smoke and documenting tobacco use should be used in every practice or healthcare service.
- **Recommendation 3** – Offer brief smoking cessation advice in routine consultations and appointments, whenever possible.
- **Recommendation 4** – Offer follow-up to all people who are attempting to quit smoking.

Pharmacotherapy for smoking cessation

- **Recommendation 5** – 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.
- **Recommendation 6** – Combination nicotine replacement therapy (NRT) (i.e. patch and oral form) accompanied by behavioural support is more effective than NRT monotherapy accompanied by behavioural support, and should be recommended to people who smoke who have evidence of nicotine dependence.
- **Recommendation 7** – For people who have stopped smoking at the end of a standard course of nicotine replacement therapy (NRT), clinicians may consider recommending an additional course of NRT to reduce relapse.
- **Recommendation 8 –**
  1. Nicotine replacement therapy (NRT) is safe to use in patients with stable cardiovascular disease.
  2. NRT should be used with caution in patients who have had a recent myocardial infarction, unstable angina, severe arrhythmias or recent cerebrovascular events.

- **Recommendation 9** – For women who are pregnant and unable to quit smoking with behavioural support alone, clinicians might recommend nicotine replacement therapy (NRT), compared with no NRT. Behavioural support and monitoring should also be provided.
- **Recommendation 10 –** Varenicline should be recommended to people who smoke and who have been assessed as clinically suitable for this medication; it should be provided in combination with behavioural support.
- **Recommendation 11 –** For people who have abstained from smoking after a standard course of varenicline in combination with behavioural support, clinicians may consider a further course of varenicline to reduce relapse.
- **Recommendation 12** – For people who are attempting to quit smoking using varenicline accompanied by behavioural support, clinicians might recommend the use of varenicline in combination with nicotine replacement therapy, compared with varenicline alone.
- **Recommendation 13 –** Bupropion sustained release should be recommended to people who smoke and who have been assessed as clinically suitable for this medication; it should be provided in combination with behavioural support. Bupropion is less effective than either varenicline or combination nicotine replacement therapy.
- **Recommendation 14 –** Nortriptyline should be considered as a second-line smoking cessation pharmacotherapy agent because of its adverse effects profile.
- **Recommendation 15** – Nicotine-containing e-cigarettes are not first-line treatments for smoking cessation. The strongest evidence base for efficacy and safety is for currently approved pharmacological therapies combined with behavioural support. The lack of approved nicotine-containing e-cigarette products creates an uncertain environment for patients and clinicians, as the constituents of the vapour produced have not been tested and standardised. However, for people who have tried to achieve smoking cessation with approved pharmacotherapies but failed, and who are still motivated to quit smoking and have brought up e-cigarette usage with their healthcare practitioner, nicotine-containing e-cigarettes may be a reasonable intervention to recommend. This needs to be preceded by an evidence-informed shared decision-making process, whereby the patient is aware of the following:
  - no tested and approved e-cigarette products are available
  - the long-term health effects of vaping are unknown
  - possession of nicotine-containing e-liquid without a prescription is illegal
  - in order to maximise possible benefit and minimise risk of harms, only short-term use is recommended
  - dual use (i.e. with continued tobacco smoking) needs to be avoided.

Recommendation 16 – Referral to telephone call-back counselling services should be offered to all people who smoke.

1.1.2. International guidelines

International Guidelines, including RACGP, are included and summarised in **Table 1.**

Table 1: Recommendations from international guidelines

Guideline	Date of guideline	Structured approach*	Pharmacotherapy										Behaviour/ counsell. + pharmaco.	Ref.
			BUP	BUP+NRT	CLON	CYT	NOR	NRT	NRT_{com}	VAR	VAR + NRT	VAR+BUP		
AARC	2014	5As; 5Rs: AAR	✓	Phys. Sup.	BP		Caution CVD	✓	✓	✓	Incr. SE		✓	AARC, 2014
ACC	2018	Ask about tobacco use; assess; advise; offer & connect to treatment; follow-up	**Outpatient with Stable CVD**										✓	Barua *et al*, 2018
			✓2nd	Sing. Insuff.			✓3rd	✓2nd	✓1st	✓1st	Sing. Insuff.	Sing. Insuff.		
			Inpatient with ACS											
			✓3rd						Hosp; ✓2nd (discharge)	✓1st (discharge)				
CAN ADAPTT	n.d.	5As	✓					✓		✓			✓	CAMH, nd
CDC	2016	5As	✓	✓				✓	✓	✓			✓	CDC, 2016
EPA	2014	Record smoking status; Set the time of the intervention; Give counselling; Offer drug treatment with a first-line product; Contact within first days after quit day; Relapse prevention and management	✓1st					✓1st		✓1st			✓	Rüther *et al*, 2014
HPB-MOH, Singapore	2013	Level 1: ABC Level 2: 5As Level 3: Intensive behavioural support	✓	✓				✓	✓	✓	✓		✓	HPB-MOH, Singapore, 2013
Jordan	n.d.	1A) Brief advice: ask; advise; and refer; or ask; advise; assess; assist; or 2) face-to-face support - additional through intensive counseling	ü1st	✓	✓2nd	Mentioned	✓2nd	✓1st	✓	✓1st	✓		✓	Hawari, n.d.

Guideline	Date of guideline	Structured approach*	Pharmacotherapy										Behaviour/ counsell. + pharmaco.	Ref.
			BUP	BUP+NRT	CLON	CYT	NOR	NRT	NRT_{com}	VAR	VAR + NRT	VAR+BUP		
		sessions possibly accompanied by medication use												
Ministry of Health and Family Welfare, India	2011	5As; 5Rs	✓					✓	✓	✓			✓	Ministry of Health and Family Welfare, India, 2011
Ministry of Health, Malaysia	n.d.	5As; 5Rs	✓	✓		Mentioned	✓	✓	✓	✓	Incr. SE		✓	Ministry of Health, Malaysia, n.d.
NCCN	2016	Assess; engage in motivational dialogue; if ready to quit within 4 weeks establish quit plan, set quit date and provide smoking cessation therapy, and if not ready to quit assess barriers and concerns and establish future quit date and encourage initiation of pharmacotherapy	✓2nd	✓2nd	Ongoing		Ongoing		✓1st	✓1st	Ongoing	Ongoing	✓	Shields *et al*, 2016
NHS, Scotland	2017	Brief intervention: ask; advise; if smoker wants to quit, offer referral to specialist quit service. If not accepted provide pharmacotherapy and additional support; if do not want to quit encourage to seek help in future	✓					✓	✓	✓			✓	NHS Scotland, 2017

Guideline	Date of guideline	Structured approach*	Pharmacotherapy										Behaviour/ counsell. + pharmaco.	Ref.
			BUP	BUP+NRT	CLON	CYT	NOR	NRT	NRT_{com}	VAR	VAR + NRT	VAR+BUP		
NHS	2019	Ask; brief advice						✓		✓				NHS, 2019
NICE	2018	Ask; brief advice	✓					✓		✓			✓	NICE, 2018
NZ Governme nt	2014	ABC	✓				✓	✓		✓			✓	NZ Government, 2014
RACGP	2019	Brief intervention: Ask; advise; help Comprehensive intervention5As	✓1st		Mentioned	Mentioned	✓2nd	✓1st	✓1st	✓1st	✓		✓	RACGP, 2019
RCGP and RCP	2014	Not included	✓	✓		✓	✓		✓	✓			✓	RCGP & RCP, 2014
South Africa	2013	Ask; alert; assess; assist/arrange	✓		✓		✓		✓	✓			✓	van Zyl-Smit *et al*, 2013
US Departme nt of Health and Human Services, 2008	2008	5As	✓1st	✓	✓2nd		✓2nd		✓1st	✓1st			✓	US Department of Health and Human Services, 2008

**Structured approaches:*

5As: ***A****sk about tobacco use;* ***A****dvise to quit;* ***A****ssess willingness to quit;* ***A****ssist in quitting – smoking cessation treatment and interventions to increase quitting;* ***A****rrange follow-up;*

AAR: ***A****sk about tobacco use;* ***A****dvise to quit smoking;* ***R****efer to smoking cessation services*

ABC: ***A****sk about tobacco use;* ***B****rief advice;* ***C****essation support*

5Rs: ***R****elevance;* ***R****isks;* ***R****ewards;* ***R****oadblocks;* ***R****epetition (to be emphasised*

Abbreviations: ✓, included; ✓1st, included as first-line; ✓2nd, included as second-line; ✓3rd, included as third-line

AARC, American Association of Respiratory Care; ACC, American College of Cardiology; ACS, acute coronary syndrome; Behaviour/counsel + pharmaco, behavioural therapy or counselling in combination with pharmacotherapy; BP, caution blood pressure decrease; BUP, bupropion; CAMH, Centre for Addiction and Mental Health; CLON, clonidine; CVD, cardiovascular disease; CYT, cytisine; EPA, European Psychiatric Association; hosp., hospitalisation; Incr. SE, increased side-effects; NCCN, National Comprehensive Cancer Network; NHS, National Health Service; n.d., no date; NOR, nortriptyline; NRT, nicotine replacement therapy; NRT_{comb}, NRT combination is patches and lozenges, gum, inhaler or nasal spray; Ongoing, panel acknowledges ongoing evaluation of alternatives; Phys. Supp., physician support; RCGP, Royal College of General Practitioners; Royal College of Psychiatrists; Sing. Insuffic., single agent insufficient; VAR, varenicline; VAR+NRT, varenicline + NRT

1.1.3. Summary of international guidelines

Most guidelines used a structured approach, predominantly the 5As and 5Rs to assess smoking and provide advice, assistance, counselling and smoking cessation treatments to smokers. In most cases, the benefit of a combination of behavioural therapy or counselling together with pharmacotherapy is recommended.

Many pharmacotherapy guidelines outline options without making any specific recommendations with regard to the choice of agent, with options including mainly NRT, varenicline, bupropion and combination NRT. Other guidelines specify 1st-, 2nd- and 3rd line options. First line options are predominantly varenicline, NRT and/or NRT combination therapy. In some guidelines, bupropion is not included or included as a second- or third-line option. This is in recognition of the lower efficacy and side-effects associated with bupropion.

The latest guidelines also include NRT in combination with varenicline and sometimes bupropion as treatment options. Other therapies included in guidelines are nortriptyline and clonidine, both of which are not registered for smoking cessation in Australia. Nortriptyline is indicated for the treatment of depression, while clonidine is indicated for hypertension, vascular headaches, migraine and menopausal-associated vasodilation symptoms. In addition, cytisine is not currently available in Australia as a registered therapeutic product outside of the clinical trial setting (note, available as a complementary medicine in the form of cytisus laburnum extract).

1.2 Registered indications and reimbursement restrictions for smoking cessation therapies

Table 2 outlines the registered indications and reimbursement restrictions for smoking cessation treatments.

1.2.1 Bupropion

Bupropion is registered for short-term adjunctive therapy for smoking cessation in patients committed to quit smoking in conjunction with counselling.

In terms of reimbursement, bupropion has two Pharmaceutical Benefit Scheme (PBS)-listings, both of which are Authority Required (streamlined). The first is for commencement of treatment and the second for completion of treatment.

Bupropion is only permitted as sole PBS-subsidised therapy and only 9 weeks of treatment is permitted per 12 month period. In addition, there must be a period of 6 months between commencing a course of bupropion and varenicline.

Patients accessing bupropion must have indicated that they are committed to stopping smoking and they must undergo concurrent counselling.

1.2.2 Nicotine replacement therapy

NRT (patches, gum, lozenges, sprays and inhalers) are registered for smoking cessation in smokers who are nicotine dependent and are committed to quit smoking in conjunction with counselling.

NRT has restricted benefit PBS-listings for nicotine dependence: 1) as sole PBS-subsidised therapy in Aboriginal and Torres Strait Islanders, and 2) sole PBS-subsidised therapy in smokers who have indicated that they are committed to quit smoking and are undergoing counselling.

Only 12 weeks of nicotine replacement therapy is permitted per year.

It is important to note that Step 1, Step 2 and Step 3 NRT is reimbursed, despite the fact that the RACGP indicates that weaning off NRT is not supported by the evidence.

1.2.5 Varenicline

Varenicline is registered as an aid to smoking cessation in adults over the age of 18 years.

In terms of reimbursement, varenicline has three PBS-listings, all of which are Authority Required (streamlined). The first is for commencement of treatment, the second for continuation of treatment and the third is for completion of treatment in patients who have quit after the first 12 weeks of treatment.

Varenicline is only permitted as sole PBS-subsidised therapy and only 24 weeks of treatment is permitted per 12 month period. In addition, there must be a period of 6 months between commencing a course of bupropion and varenicline and between two courses of varenicline.

Individuals accessing varenicline must have indicated that they are committed to stopping smoking and they must undergo concurrent counselling.

Table 2: Registered indications and reimbursed restrictions for smoking cessation therapies

Smoking cessation agent	TGA indication	PBS listing					
		Item code	Form and strength	Max Quantity	No. of repeats	Note	Restriction
Bupropion	Short-term adjunctive therapy for treatment of nicotine dependence in those who are committed to quitting smoking, when used in conjunction with counselling for smoking cessation/abstinence	8465M	150 mg modified release tablets	30	0	• Clinical review is recommended within 2 to 3 weeks of the original prescription being requested. • The period between commencing a course of bupropion and varenicline tartrate must be at least 6 months. • A patient may only qualify for PBS-subsidised treatment under this treatment phase restriction once during a short-term course of treatment. • No increase in the maximum quantity or number of units may be authorised • No increase in the number of repeats may be authorised.	**Authority Required (STREAMLINED)** 6882 Nicotine dependence Treatment phase: Commencement of a short term (9 weeks course of treatment) **Clinical criteria:** • 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 9 weeks of PBS-subsidised treatment with this drug per 12-month period. **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 treatment is initiated. Details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated.
		8710K		90	0	• Clinical review is recommended within 2 to 3 weeks of the original prescription being requested. • The period between commencing a course of bupropion and varenicline tartrate must be at least 6 months. • No increase in the maximum quantity or number of units may be authorized • No increase in the number of repeats may be authorised.	**Authority Required (STREAMLINED)** 6881 Nicotine dependence Treatment phase: Completion of a short term (9 weeks course of treatment) **Clinical criteria:** • The treatment must be as an aid to achieving abstinence from smoking, AND

Smoking cessation agent	TGA indication	PBS listing					
		Item code	Form and strength	Max Quantity	No. of repeats	Note	Restriction
							• The treatment must be the sole PBS-subsidised therapy for this condition, AND • Patient must have previously received PBS-subsidised treatment with this drug during this course of treatment, AND • Patient must not receive more than 9 weeks of PBS-subsidised treatment with this drug per 12-month period. **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 treatment is initiated.
Nicotine replacement therapy • Use as an aid in the cessation of smoking in smokers with nicotine dependence; and • Relief of nicotine withdrawal symptoms, including nicotine cravings, associated with smoking cessation		10076H	25 mg/16 hours Patch	28	2	• No increase in the maximum quantity or number of units may be authorised • No increase in the number of repeats may be authorised.	**Restricted benefit** Nicotine dependence **Population criteria:** • Patient must be an Aboriginal or a Torres Strait Islander person. **Clinical criteria:** • The treatment must be the sole PBS-subsidised therapy for this condition. **Note** 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. **Restricted Benefit** Nicotine dependence **Clinical criteria:** • The treatment must be as an aid to achieving abstinence from smoking, **AND**
		11612E	4 mg chewing gum	216	2		
		11617K	2 mg lozenges	216	2		
		11618L	2 mg chewing gum	432 (2 packs)	1		
		11619M	4 mg lozenge	216	2		
		5465P	21 mg/24 hours Patch	28	2		

Smoking cessation agent	TGA indication	PBS listing					
		Item code	Form and strength	Max Quantity	No. of repeats	Note	Restriction
							• 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. **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. Details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated.
		5573H	7 mg/24 hours Patch	28	2		**Restricted Benefit** Nicotine dependence **Clinical criteria:** • 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. **Treatment criteria:** • Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling
		5572G	14 mg/24 hours Patch	28	2		
		3414Q	21 mg/24 hours Patch	28	2		

Smoking cessation agent	TGA indication	PBS listing					
		Item code	Form and strength	Max Quantity	No. of repeats	Note	Restriction
							program or is about to enter such a program at the time PBS-subsidised treatment is initiated. Details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated.
		5571F	21 mg/24 hours Patch	28	2	• 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 or number of units may be authorised • No increase in the number of repeats may be authorised.	**Restricted benefit** Nicotine dependence **Population criteria:** • Patient must be an Aboriginal or a Torres Strait Islander person. **Clinical criteria:** The treatment must be the sole PBS-subsidised therapy for this condition.
Varenicline	Aid to smoking cessation in adults over the age of 18 years	9128K	Tablets 500 µg 1 mg	 11 42	0	• 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 • A patient may only qualify for PBS-subsidised treatment under this treatment phase restriction once during a short-term course of treatment. • No increase in the maximum quantity or number of units may be authorised. • No increase in the maximum number of repeats may be authorised.	**Authority Required (STREAMLINED)** 6871 Nicotine dependence **Treatment Phase**: Commencement of a short-term (12 weeks or 24 weeks) course of treatment **Clinical criteria:** • 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. **Treatment criteria:** • Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling

Smoking cessation agent	TGA indication	PBS listing					
		Item code	Form and strength	Max Quantity	No. of repeats	Note	Restriction
							program or is about to enter such a program at the time PBS-subsidised treatment is initiated. Details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated. Clinical review is recommended within 2 to 3 weeks of the initial prescription being requested.
		9129L	1 mg tablets	112 (2 packs)	0	• A course of treatment with this drug is 12 weeks or up to 24 weeks, if initial treatment of 12 weeks has been successful. • A patient may only qualify for PBS-subsidised treatment under this treatment phase restriction once during a short-term course of treatment. • No increase in the maximum quantity or number of units may be authorised. • No increase in the maximum number of repeats may be authorised.	**Authority Required (STREAMLINED)** 7483 Nicotine dependence **Treatment Phase**: Continuation of a short-term (12 weeks or 24 weeks) course of treatment **Clinical criteria:** • 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 previously received treatment with this drug during this current course of treatment. **Treatment criteria:** • Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program.
		5496W	1 mg tablets	56	2		**Authority Required (STREAMLINED)** 6885 Nicotine dependence **Treatment Phase**: Completion of a short-term (24 weeks) course of treatment **Clinical criteria:** • The treatment must be as an aid to achieving abstinence from smoking, **AND**

Smoking cessation agent	TGA indication	PBS listing					
		Item code	Form and strength	Max Quantity	No. of repeats	Note	Restriction
							• The treatment must be the sole PBS-subsidised therapy for this condition, **AND** • Patient must have previously received PBS-subsidised treatment with this drug during this current course of treatment, **AND** • 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 current course of treatment. **Treatment criteria:** • Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program.

1.3 Difference between guidelines and registration and reimbursement of smoking cessation therapies

Bupropion, NRT and varenicline are registered and reimbursed for smoking cessation in Australia. Bupropion has been PBS-listed since 1 February 2001 and varenicline since 1 January 2008. Nicotine patches were listed on the PBS for Aboriginal and Torres Strait Islander Individuals from 1 December 2008 and for all Australian smokers from 1 February 2011. Nicotine gum and lozenges were listed on the PBS from 1 February 2019.

In alignment with the guidelines, reimbursement of bupropion, NRT, with the exception of Aboriginal and Torres Strait Islanders, and varenicline require the patient to be committed to stopping smoking and be enrolled in a counselling program. For Aboriginal and Torres Strait Islanders it is noted that benefit of NRT is improved with a counselling program.

Unlike the guidelines, the restrictions stipulate a maximum period of treatment per year of 9 weeks for bupropion, 12 weeks for NRT and 24 weeks for varenicline if individuals who have ceased smoking at 12 weeks are prescribed the additional 12 weeks course to increase the chance of long-term cessation, alternatively the treatment period is 12 weeks. In addition, the restriction also stipulates that there must be a period of 6 months between commencing a course of bupropion and varenicline and six months between courses of varenicline which is also not included in the guidelines.

Finally, the PBS-listings stipulate that bupropion, NRT and varenicline are to be used as sole PBS-subsidised treatments whereas the guidelines recommend combination NRT, and many include combination varenicline and NRT and bupropion and NRT in some cases.

2. Review the utilisation of PBS-listed medicines for smoking cessation including but not limited to patient demographics, time on treatment, and the proportion using PBS subsidised combination treatment.

PBS 1 in 10 data on varenicline usage were reviewed.

2.1 Line of therapy of varenicline

Varenicline initiations by line of therapy are shown in **Figure 1**. Initiations are all individuals who commence a line of therapy with varenicline. Lines of therapy are defined when a patient changes molecule or there is a 4 month break between scripts. The figure shows that in 2019, 27% of varenicline initiations were first-line, 20% were second-line, 15% were third-line, 11% were fourth-line, 8% were fifth-line and 19% were ≥6th line.

Figure 2 shows all varenicline scripts by line of therapy. In 2019, of the total scripts (353,980), the breakdown was as follows: first-line - 79,010 (22%); second-line - 65,880 (19%) scripts; third-line - 52,900 (15%) scripts; fourth-line - 41,700 (12%); fifth-line - 31,940 (9%) and ≥ sixth-line - 82,550 (23%).

2.2 Varenicline use by restriction

Varenicline use by restriction is included in **Table 3.** It is important to note that for completion, the restriction is for one plus three repeats therefore, whereas the services for initiation and continuation represent an individual, three services for completion could represent one individual. It is important to note that the uptake under the restriction for completion is low.

Table 3: Varenicline use by restriction

	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Total
Initiation	11,711	13,561	14,435	10,812	12,213	12,581	10,989	12,349	13,390	13,460	14,267	11,763	**151,531**
Continuation	4,621	5,174	6,148	4,982	5,280	5,418	4,731	5,064	5,133	5,192	5,935	5,375	**63,053**
Completion	6,293	6,432	7,680	6,213	6,963	7,157	6,338	6,794	6,912	6,948	7,648	7,504	**82,882**

2.3 Age of individuals using varenicline for smoking cessation

Ages of individuals initiated on treatment with varenicline in 2019 are included in **Figure 3** and of individuals who filled all varenicline scripts are included in **Figure 4**. These are outlined in **Table 4**, which shows that the majority of usage is in individuals who are 35-49 years and 50-64 years.

Table 4: Ages of individuals taking varenicline for smoking cessation

	Initiations on varenicline		All varenicline scripts	
	Number	%	Number	%
<35 years	35,230	22%	61,750	17%
35-49 years	56,670	35%	121,590	34%
50-64 years	50,400	32%	124,380	35%
≥65 years	17,500	11%	46,260	13%
Total	159,800		353,980	

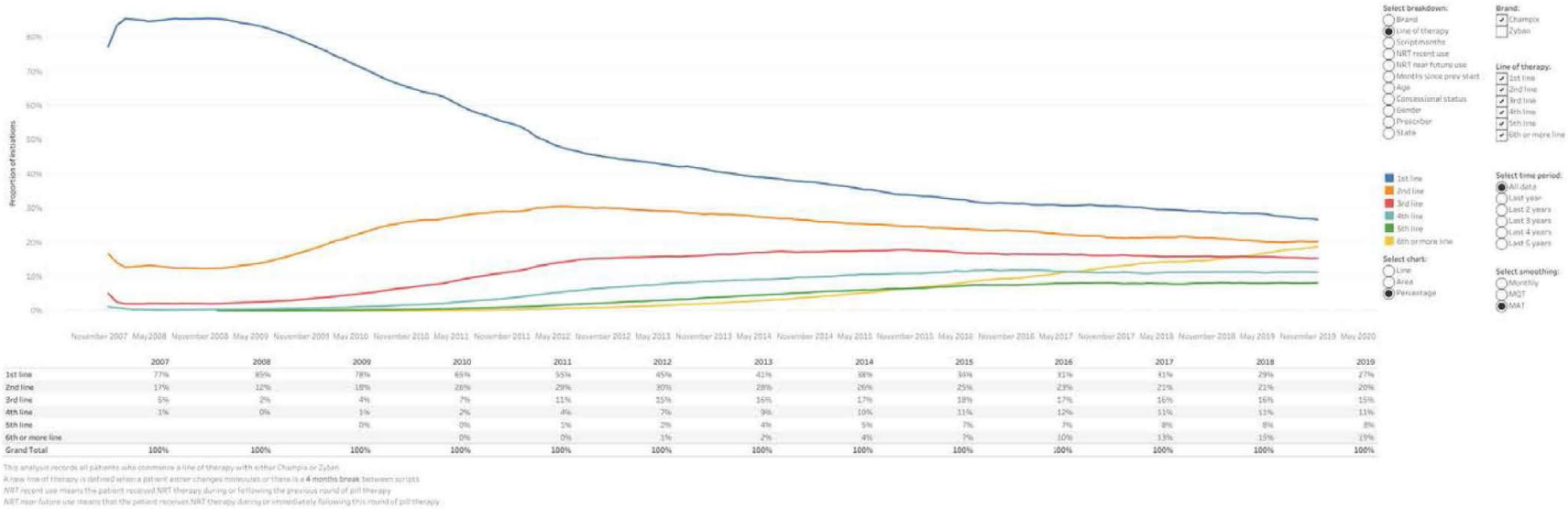
2.4 Gender of individuals using varenicline for smoking cessation

The gender of individuals initiated on treatment with varenicline in 2019 are included in **Figure 5** and of individuals who filled all varenicline scripts are included in **Figure 6**. Of individuals initiating varenicline 55% were male and 56% of all varenicline scripts were for males.

2.5 Combination therapy with nicotine replacement therapy

Figure 7 shows that only 11% of individuals initiating varenicline had recently received PBS-reimbursed nicotine replacement therapy and as shown in **Figure 8**, 4% of individuals who had been initiated on varenicline received nicotine replacement therapy soon afterwards. These analyses could be assumed to indicate combination use. However, it is important to note that nicotine replacement therapy may be purchased privately without a prescription and used with varenicline, thereafter, combination use may be higher than shown here.

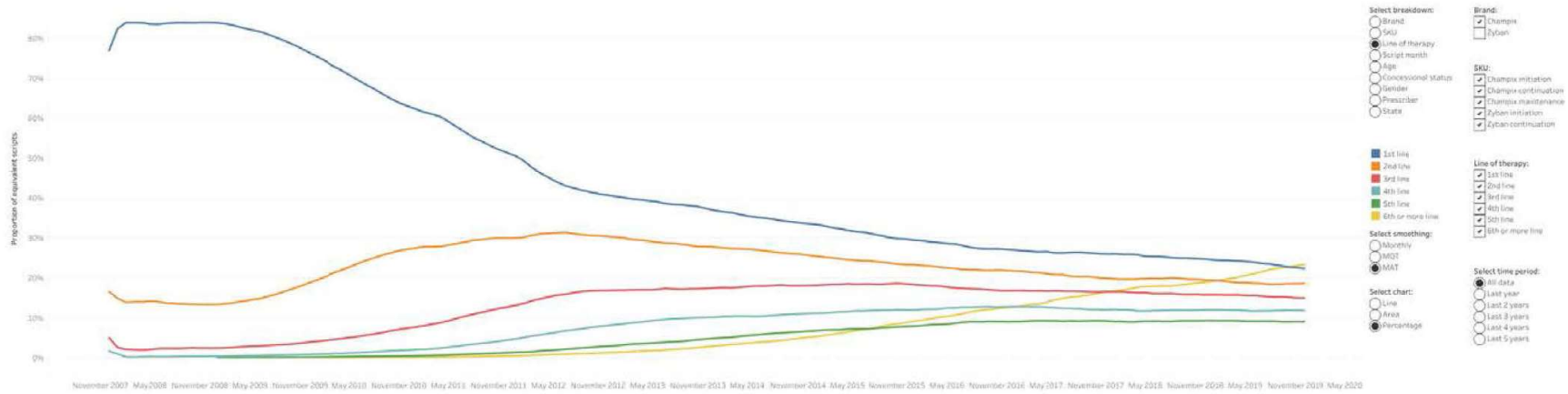
In addition, PBS data do not capture patient-specific usage of smoking cessation therapies for Aboriginal people and Torres Strait Islanders under the Section 100 Remote Area Aboriginal Health Service measure. As indicated in the submission by NACCHO and supported by Pfizer, this population has considerably higher smoking rates and a demonstrated need for enhanced access to combination therapy including varenicline + NRT. Existing usage of this varenicline + NRT combination therapy is not currently captured in the statistics.



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
1st line	77%	89%	78%	65%	55%	45%	41%	38%	36%	31%	31%	29%	27%
2nd line	17%	12%	18%	26%	29%	30%	28%	26%	25%	23%	21%	21%	20%
3rd line	5%	2%	4%	7%	11%	15%	16%	17%	18%	17%	16%	16%	15%
4th line	1%	0%	1%	2%	4%	7%	9%	10%	11%	12%	11%	11%	11%
5th line			0%	0%	1%	2%	4%	5%	7%	7%	8%	8%	8%
6th or more line				0%	0%	1%	2%	4%	7%	10%	13%	15%	19%
Grand Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

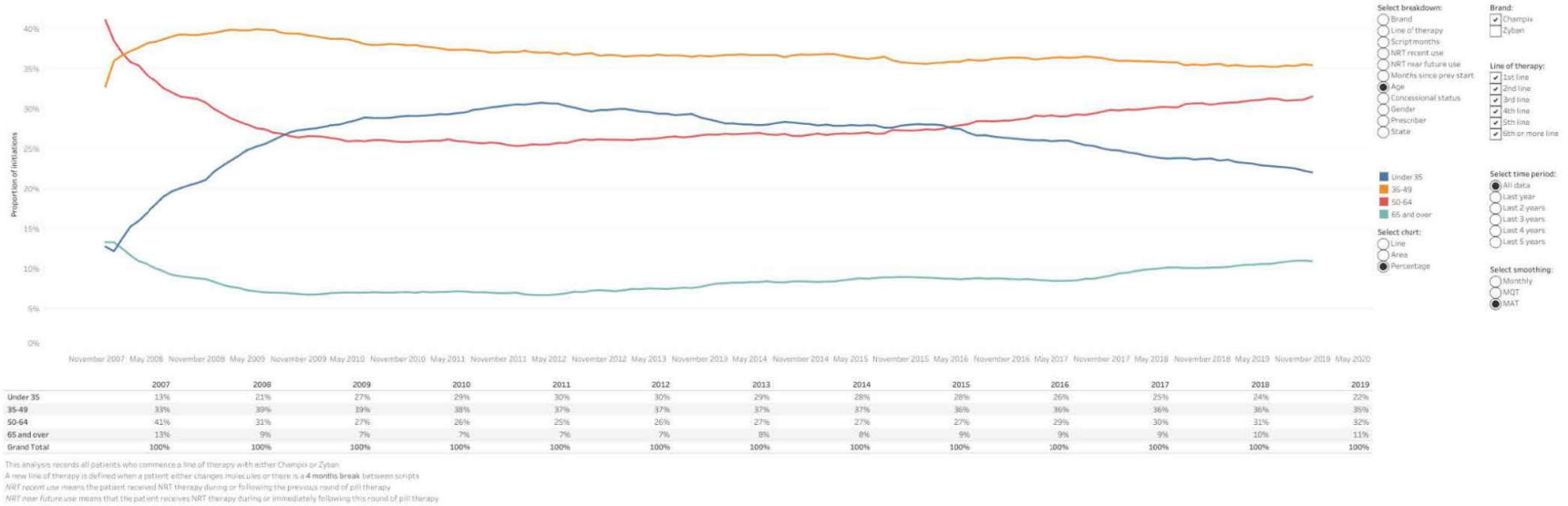
This analysis records all patients who commence a line of therapy with either Champix or Zyban
A new line of therapy is defined when a patient either changes molecules or there is a **4 months break** between scripts
NRT recent use means the patient received NRT therapy during or following the previous round of pill therapy
NRT near future use means that the patient received NRT therapy during or immediately following this round of pill therapy

Figure 1: Varenicline initiations by line of therapy



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
1st line	77%	84%	76%	63%	51%	41%	37%	34%	30%	27%	26%	25%	22%
2nd line	16%	13%	19%	27%	30%	30%	28%	26%	23%	22%	20%	19%	19%
3rd line	5%	2%	4%	7%	13%	17%	17%	18%	18%	17%	17%	16%	15%
4th line	2%	0%	1%	2%	4%	8%	10%	11%	12%	13%	12%	12%	12%
5th line			0%	0%	1%	3%	6%	7%	8%	9%	9%	9%	9%
6th or more line				0%	0%	1%	3%	5%	9%	13%	16%	19%	23%
Grand Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

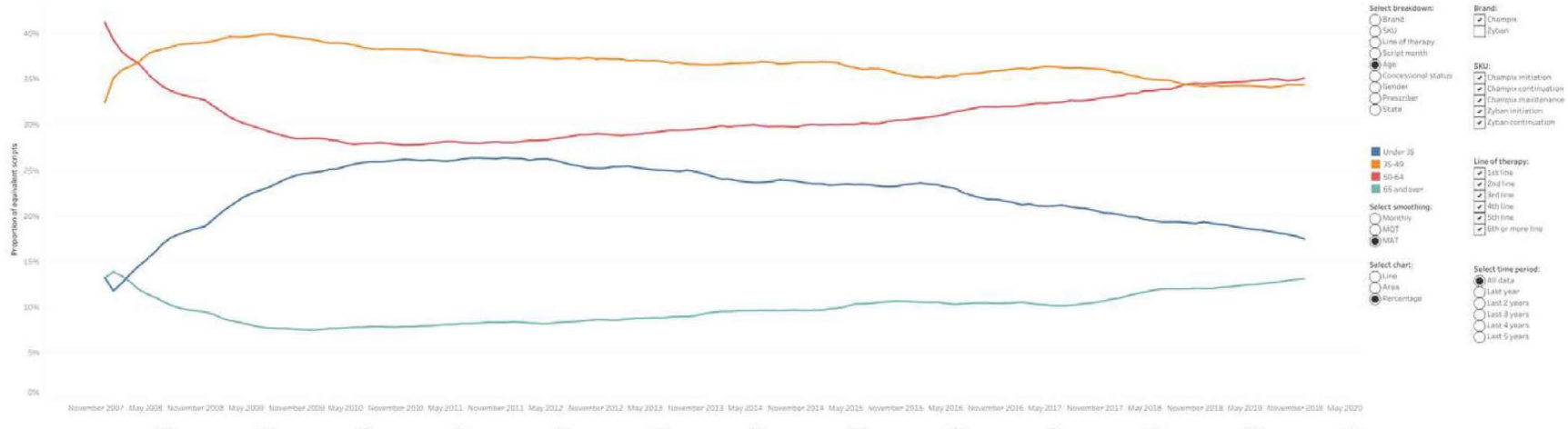
Figure 2: Varenicline scripts by line of therapy



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Under 35	13%	21%	27%	29%	30%	30%	29%	28%	28%	26%	25%	24%	22%
35-49	33%	39%	39%	38%	37%	37%	37%	37%	36%	36%	36%	36%	35%
50-64	41%	31%	27%	26%	25%	26%	27%	27%	27%	29%	30%	31%	32%
65 and over	13%	9%	7%	7%	7%	7%	8%	8%	9%	9%	9%	10%	11%
Grand Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

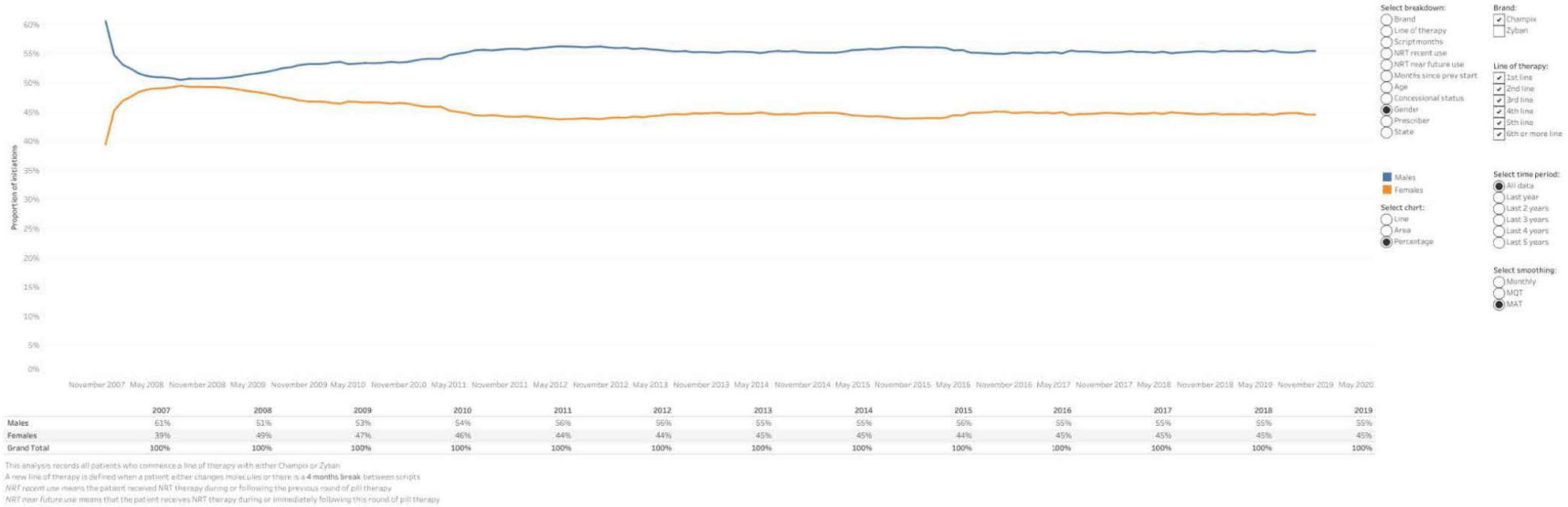
This analysis records all patients who commence a line of therapy with either Champix or Zyban
A new line of therapy is defined when a patient either changes molecules or there is a **4 months break** between scripts
NRT recent use means the patient received NRT therapy during or following the previous round of pill therapy
NRT near future use means that the patient receives NRT therapy during or immediately following this round of pill therapy

Figure 3: Age of individuals initiating varenicline



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Under 35	13%	19%	25%	26%	26%	25%	25%	24%	23%	22%	20%	19%	17%
35-49	32%	39%	39%	38%	37%	37%	37%	37%	35%	36%	36%	34%	34%
50-64	41%	33%	28%	28%	28%	29%	30%	30%	31%	32%	33%	34%	35%
65 and over	13%	9%	7%	8%	8%	9%	9%	10%	11%	10%	11%	12%	13%
Grand Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

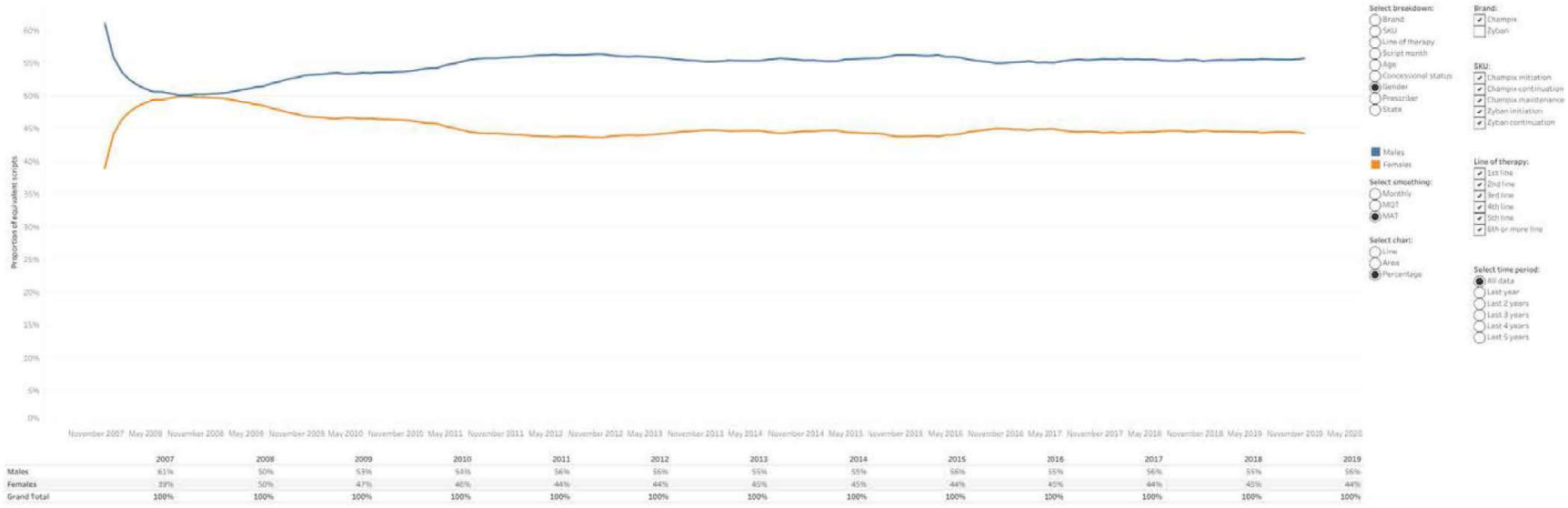
Figure 4: Age of individuals filling scripts for varenicline



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Males	61%	51%	53%	54%	56%	56%	55%	55%	56%	55%	55%	55%	55%
Females	39%	49%	47%	46%	44%	44%	45%	45%	44%	45%	45%	45%	45%
Grand Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

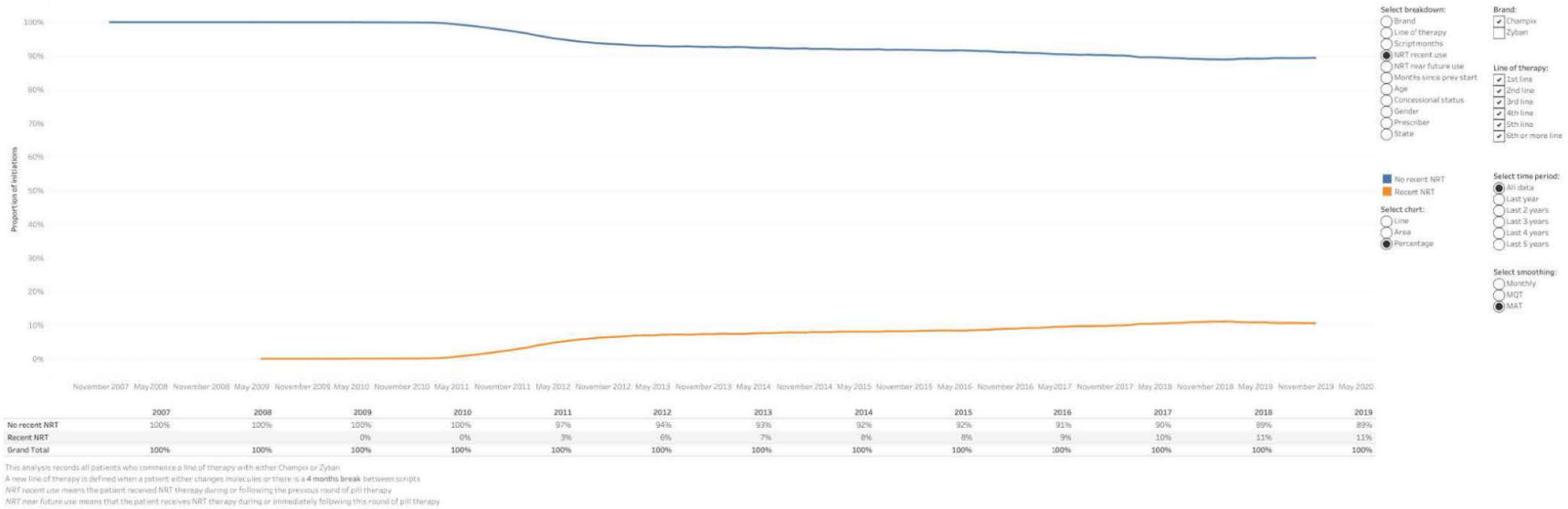
This analysis records all patients who commence a line of therapy with either Champix or Zyban
A new line of therapy is defined when a patient either changes molecules or there is a **4 months break** between scripts
NRT recent use means the patient received NRT therapy during or following the previous round of pill therapy
NRT near future use means that the patient receives NRT therapy during or immediately following this round of pill therapy

Figure 5: Gender of individuals initiating varenicline



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Males	61%	50%	53%	54%	56%	56%	55%	55%	56%	55%	56%	55%	56%
Females	39%	50%	47%	46%	44%	44%	45%	45%	44%	45%	44%	45%	44%
Grand Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

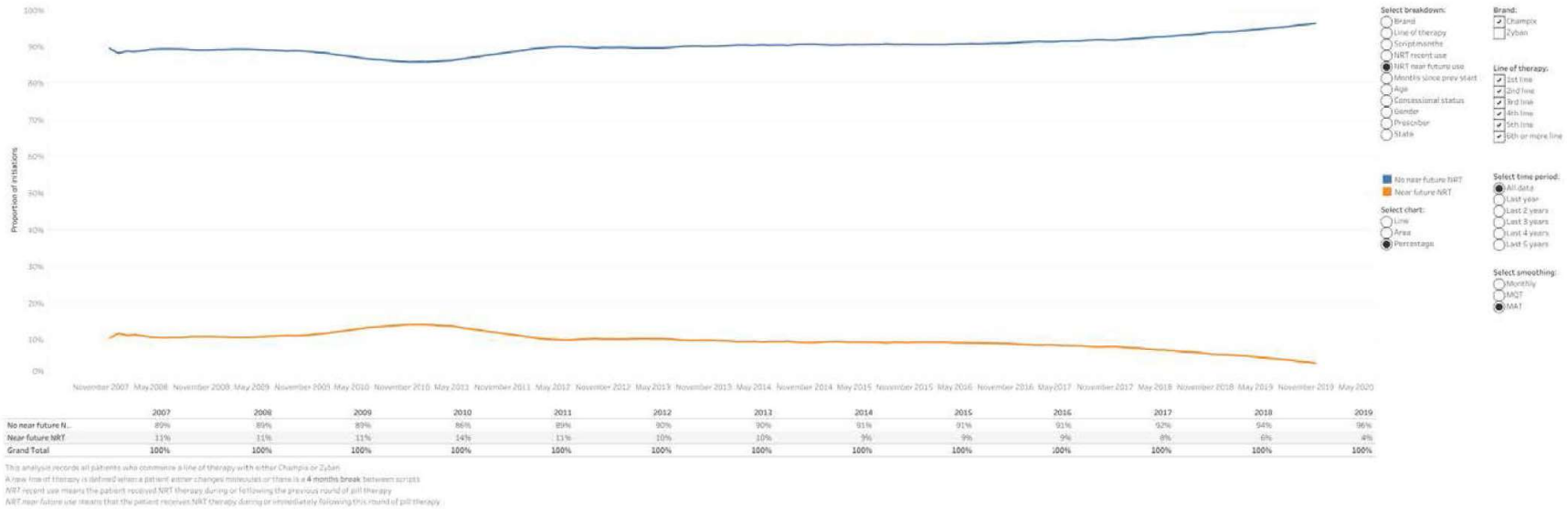
Figure 6: Gender of individuals filling scripts for varenicline



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
No recent NRT	100%	100%	100%	100%	97%	94%	93%	92%	92%	91%	90%	89%	89%
Recent NRT			0%	0%	3%	6%	7%	8%	8%	9%	10%	11%	11%
Grand Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

This analysis records all patients who commence a line of therapy with either Champix or Zyban
A new line of therapy is defined when a patient either changes molecules or there is a **4 months break** between scripts
NRT recent use means the patient received NRT therapy during or following the previous round of pill therapy
NRT near future use means that the patient receives NRT therapy during or immediately following this round of pill therapy

Figure 7: Varenicline initiations with recent NRT use



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
No near future N...	89%	89%	89%	86%	89%	90%	90%	91%	91%	91%	92%	94%	96%
Near future NRT	11%	11%	11%	14%	11%	10%	10%	9%	9%	9%	8%	6%	4%
Grand Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

This analysis records all patients who commence a line of therapy with either Champix or Zyban.
A new line of therapy is defined when a patient either changes molecules or there is a **4 months break** between scripts
NRT recent use means the patient received NRT therapy during or following the previous round of pill therapy
NRT near future use means that the patient received NRT therapy during or immediately following this round of pill therapy

Figure 8: Varenicline initiations with near future NRT use

3. Review the efficacy and safety of nicotine replacement therapy, varenicline and bupropion for smoking cessation including combination therapies not currently PBS subsidized

3.1 Introduction

A systematic literature review was performed to identify clinical studies demonstrating the efficacy and safety of varenicline including

- Randomised controlled and other clinical studies of varenicline
- Compared to placebo, NRT and bupropion as well as relevant non-comparative studies, and
- As monotherapy and in combination with NRT.

Four studies were identified as pivotal clinical evidence. A further forty-six publications were identified which included forty new studies. Finally, four combination studies were identified.

3.2 Varenicline compared to bupropion and nicotine replacement therapy

3.2.1 Pivotal clinical evidence

Four direct randomised trials provide evidence of the comparative benefit of varenicline as an aid to smoking cessation.

The latest clinical evidence compared treatment with varenicline, bupropion and nicotine patches and provides the most updated efficacy and safety data of the comparison of these three types of smoking cessation therapy. The citation for this clinical study is:

> Anthenelli RM, Benowitz NL, West R, Aubin LS, McRae T, Lawrence D, Ascher J, Russ C, Krishen A and Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. The Lancet. Published online April 22, 2016.

Two trials employed three treatment arms to evaluate the efficacy of both the active non-nicotine pharmacotherapies for smoking cessation (varenicline and bupropion) vs. placebo. The citations for the two trials follow.

> Gonzales D, Rennard S, Nides M, Oncken C, Azoulay S, Billing C, Watsky E, Gong J, Williams K, Reeves K. Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs. sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. Journal of the American Medical Association, 2006; 296(1): 47-55.
>
> Jorenby D, Hays J, Rigotti N, Azoulay S, Watsky E, Williams K, Billing C, Gong J, Reeves K. Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs. placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. Journal of the American Medical Association, 2006; 296(1):56-63.

Another trial employed two treatment arms to evaluate the efficacy of varenicline vs. NRT. The citation for the trial follows.

Aubin HJ, Bobak A, Britton JR, Oncken C, Billing CB Jr, Gong J, Williams KE, Reeves KR. Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomised, open-label trial. , 2008

Presented in **Table 5** is a summary of the key trials (Anthenelli *et al*, 2016; Gonzales *et al*, 2006, Jorenby *et al*, 2006; Aubin *et al*, 2008) used for clinical evidence for varenicline.

Table 5: Characteristics of the Anthenelli *et al*, 2016; Gonzales *et al*, 2006; Jorenby *et al*, 2006 and Aubin *et al*, 2008

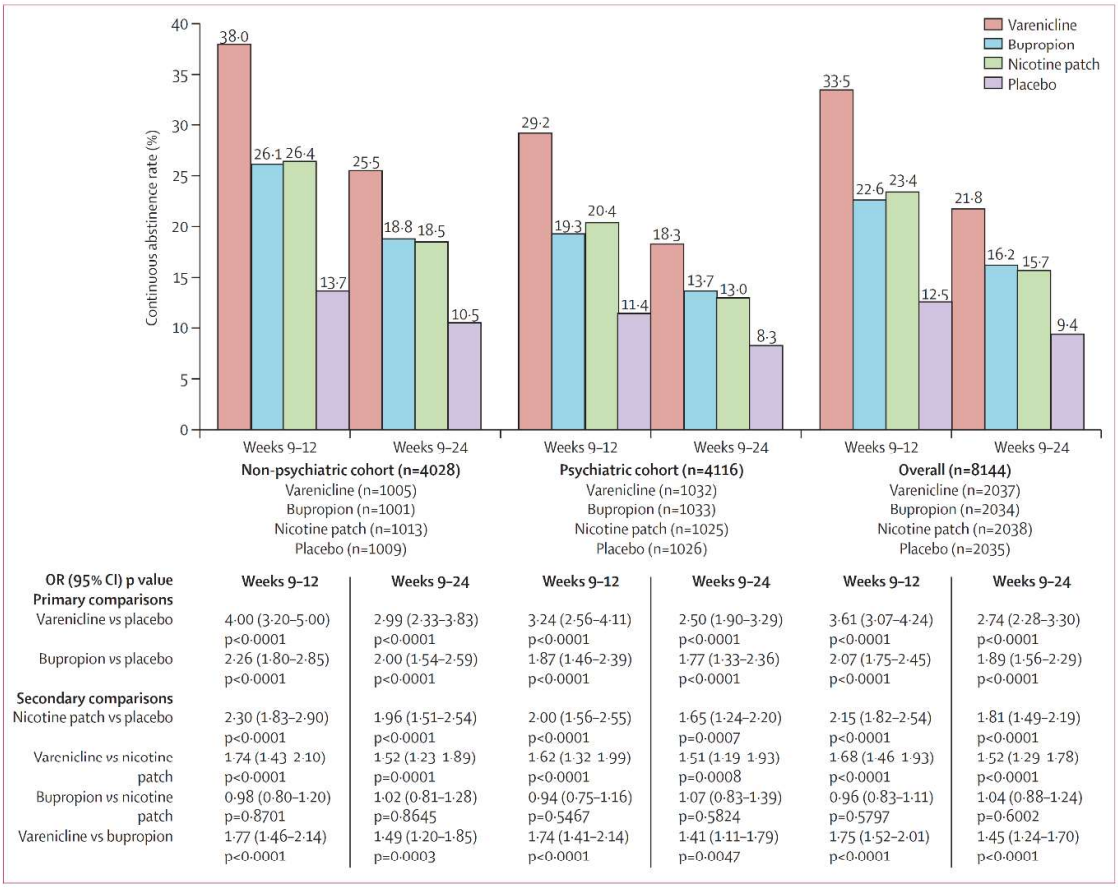
Trial identifier	Design	Treatment regimens	Patient population	Key outcome measures
Anthenelli *et al*. 2016	Randomised, double-blind, triple-dummy, placebo-controlled and active-controlled N=8144	Varenicline*: 1 mg bd Bupropion*: 150 mg bd Nicotine transdermal patch**: 21 mg daily Placebo *Treatments were appropriately up-titrated **NRT down-titrated to 14 mg daily then to 7 mg daily	Smokers, aged 18–75 years, with and without prespecified psychiatric diagnoses per DSM-IV-TR (psychiatric and non-psychiatric cohorts) who smoked an average of ≥ 10 cigarettes per day during previous year, had an exhaled carbon monoxide concentration >10 ppm at screening, and who were motivated to stop smoking	Composite measure based on post-marketing reports of neuropsychiatric adverse events in smokers taking varenicline and bupropion CAR for Weeks 9-12 CAR for Weeks 9-24 7 Day point prevalence of abstinence Other safety outcomes
Gonzales *et al*. 2006	Double-blind placebo-controlled randomised parallel multicentre study N=1,025	Varenicline: 0.5 mg/day for 3 days; 0.5 mg bd for 4 days; 1 mg bd from day 8 to 84. Bupropion: 150 mg once daily, Days 1 to 3; 150 mg bd, Days 4 to 84. Placebo: 2 tablets once daily, Days 1 to 7; 1 tablet bd Days 8 to 84.	Adults (aged 18 to 75 years) who had smoked an average of 10 cigarettes per day during the year prior to screening with no period of abstinence greater than 3 months in that time.	CQR for Weeks 9 - 12 CAR from Weeks 9 - 52 Safety
Jorenby *et al*. 2006	Double-blind placebo-controlled randomised parallel multicentre study N=1,027	Varenicline: 0.5 mg/day for 3 days; 0.5 mg bd for 4 days; 1 mg bd from day 8 to 84. Bupropion: 150 mg once daily, Days 1 to 3; 150 mg bd, Days 4 to 84. Placebo: 2 tablets once daily, Days 1 to 7; 1 tablet bd Days 8 to 84.	Adults (aged 18 to 75 years) who had smoked an average of 10 cigarettes per day during the year prior to screening with no period of abstinence greater than 3 months in that time.	CQR for Weeks 9-12 CAR from Weeks 9 - 52 Safety
Aubin *et al*. 2008	Open-label randomised multicentre study N=746	Varenicline: 0.5 mg/day for 3 days; 0.5 mg bd for 4 days; 1 mg bd from day 8 to 84. NRT (transdermal patches): 21 mg/day for 6 weeks; 14 mg/day for 2 weeks; 7 mg/day for 2 weeks	Adults (aged 18 to 75 years), weight >45.5kg and body mass index 15-38kg/m2 who had smoked at least 15 cigarettes per day during the year prior to screening with no period of abstinence greater than 3 months in that time.	CAR for Weeks 8-11 for NRT and for Weeks 9-12 for varenicline CAR for weeks 8 – 52 for NRT and weeks 9-52 for varenicline Safety

Abbreviations: bd, one tablet twice a day; CAR, continuous abstinence rate; CQR, continuous quit rate; ppm, parts per million DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision NRT, nicotine replacement therapy;

Efficacy

Varenicline versus bupropion and NRT (Athenelli *et al*, 2016)

The continuous abstinence rates for weeks 9–12 and 9–24 by treatment and the ORs for all pairwise comparisons are presented for the combined sample as well as for the two cohorts (non-psychiatric and psychiatric cohorts) in **Figure 1**.



OR (95% CI) p value	Weeks 9–12	Weeks 9–24	Weeks 9–12	Weeks 9–24	Weeks 9–12	Weeks 9–24
Primary comparisons						
Varenicline vs placebo	4·00 (3·20–5·00) p<0·0001	2·99 (2·33–3·83) p<0·0001	3·24 (2·56–4·11) p<0·0001	2·50 (1·90–3·29) p<0·0001	3·61 (3·07–4·24) p<0·0001	2·74 (2·28–3·30) p<0·0001
Bupropion vs placebo	2·26 (1·80–2·85) p<0·0001	2·00 (1·54–2·59) p<0·0001	1·87 (1·46–2·39) p<0·0001	1·77 (1·33–2·36) p<0·0001	2·07 (1·75–2·45) p<0·0001	1·89 (1·56–2·29) p<0·0001
Secondary comparisons						
Nicotine patch vs placebo	2·30 (1·83–2·90) p<0·0001	1·96 (1·51–2·54) p<0·0001	2·00 (1·56–2·55) p<0·0001	1·65 (1·24–2·20) p=0·0007	2·15 (1·82–2·54) p<0·0001	1·81 (1·49–2·19) p<0·0001
Varenicline vs nicotine patch	1·74 (1·43 2·10) p<0·0001	1·52 (1·23 1·89) p=0·0001	1·62 (1·32 1·99) p<0·0001	1·51 (1·19 1·93) p=0·0008	1·68 (1·46 1·93) p<0·0001	1·52 (1·29 1·78) p<0·0001
Bupropion vs nicotine patch	0·98 (0·80–1·20) p=0·8701	1·02 (0·81–1·28) p=0·8645	0·94 (0·75–1·16) p=0·5467	1·07 (0·83–1·39) p=0·5824	0·96 (0·83–1·11) p=0·5797	1·04 (0·88–1·24) p=0·6002
Varenicline vs bupropion	1·77 (1·46–2·14) p<0·0001	1·49 (1·20–1·85) p=0·0003	1·74 (1·41–2·14) p<0·0001	1·41 (1·11–1·79) p=0·0047	1·75 (1·52–2·01) p<0·0001	1·45 (1·24–1·70) p<0·0001

Figure 9: Continuous abstinence rates for weeks 9-12 and 9-24

Analyses based on the all-randomised population. OR=odds ratio

Source: Anthenelli et al, 2016 Figure 3

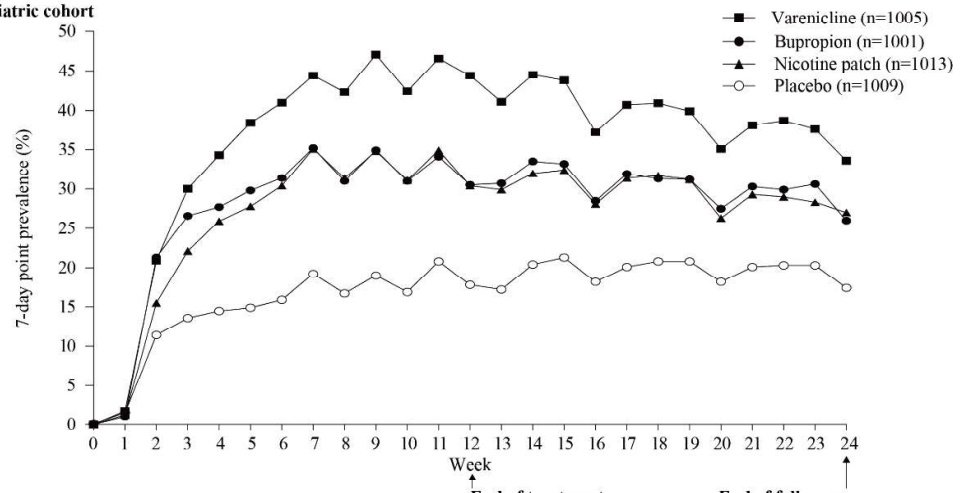
Varenicline was superior to bupropion, NRT patch and placebo at the end of treatment (weeks 9–12) and follow-up (weeks 9–24).

Bupropion was similar in efficacy to NRT patch and bupropion and NRT patch were superior to placebo

The study protocol specified that an analysis be undertaken to assess whether treatment efficacy varied between the non-psychiatric cohort and psychiatric cohort, and although the abstinence rates are lower in the psychiatric cohort versus non-psychiatric cohort (**Figure 1**), no evidence was found for an interaction (p=0.6237).

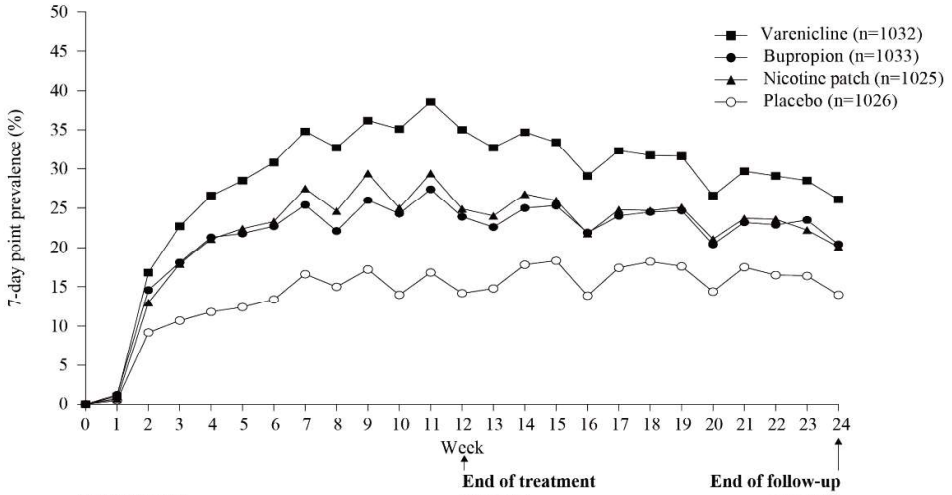
7-day point prevalence of abstinence for weeks 1–24 show results consistent with the continuous abstinence rates (**Figure 2**).

A Non-psychiatric cohort



OR (95% CI)	End of treatment Week 12	End of follow-up Week 24
Primary comparisons		
Varenicline *vs* placebo	4·23 (3·40–5·25)	2·60 (2·09–3·25)
Bupropion *vs* placebo	2·07 (1·66–2·58)	1·71 (1·36–2·14)
Secondary comparisons		
Nicotine patch vs placebo	2·17 (1·75–2·71)	1·93 (1·54–2·42)
Varenicline *vs* nicotine patch	1·94 (1·60–2·37)	1·35 (1·09–1·65)
Bupropion *vs* nicotine patch	0·95 (0·78–1·16)	0·88 (0·71–1·09)
Varenicline *vs* bupropion	2·04 (1·67–2·49)	1·52 (1·24–1·88)

B Psychiatric cohort



OR (95% CI)	End of treatment Week 12	End of follow-up Week 24
Primary comparisons		
Varenicline *vs* placebo	3·34 (2·66–4·19)	2·13 (1·69–2·70)
Bupropion *vs* placebo	1·86 (1·47–2·35)	1·54 (1·21–1·96)
Secondary comparisons		
Nicotine patch *vs* placebo	1·92 (1·52–2·42)	1·51 (1·19–1·92)
Varenicline *vs* nicotine patch	1·74 (1·42–2·13)	1·41 (1·14–1·76)
Bupropion *vs* nicotine patch	0·97 (0·79–1·19)	1·02 (0·82–1·28)
Varenicline *vs* bupropion	1·80 (1·47–2·20)	1·38 (1·11–1·71)

Analyses based on the all-randomised population during treatment (weeks 1–12) and the non-treatment follow-up period (weeks 12–24). CI=confidence interval. OR=odds ratio.

Figure 10: 7-day point prevalence of abstinence

Source: Anthenelli et al, 2016 Supplementary Appendix Figure 3A

Varenicline versus bupropion (Gonzales *et al*, 2006; Jorenby *et al*, 2006)

The primary outcome in both Gonzales *et al*, 2006 and Jorenby *et al*, 2006 trials was a 4-week continuous quit rate (CQR) from week 9 to 12. In both Gonzales *et al*, 2006 and Jorenby *et al*, 2006 smokers who were randomised to receive varenicline achieved highly statistically significant superior cessation rates compared to smokers randomised to bupropion. For the direct comparison to bupropion, subjects randomised to varenicline were almost 1.5 times more likely to have ceased smoking for the 4-weeks from Week 9 to end of the course of treatment (4-week CQR Weeks 9 to 12) than smokers who were randomised to bupropion. Results are presented in more details in **Table 6**. Response rates were similar across the trials with approximately 44% of smokers on the varenicline arm reporting 4-week CQR compared to approximately 30% of smokers on the bupropion arm. A pooled analysis of the trial results for 4-week CQR Weeks 9 to 12 reported a relative risk (RR) of 1.5 (95% CI: 1.3, 1.7, p<0.00001).

The secondary outcome measure in both Gonzales *et al*, 2006 and Jorenby *et al*, 2006 was continuous abstinence (CA) from week 9 to 52. Assessment of the data showed that smokers in the varenicline arms were 1.3 to 1.5 times more likely to have continued to refrain from smoking from Week 9 to Week 52 than smokers in the bupropion arms in Gonzales *et al*, 2006 and Jorenby *et al*, 2006, respectively. The improved efficacy for varenicline versus bupropion in long term abstinence was statistically significant in Jorenby *et al*, 2006 but not in Gonzales *et al*, 2006 (p = 0.079). The reason for the difference just failing to reach statistical significance in Gonzales *et al*, 2006 is not entirely clear given that the response rates for CA Week 9 to 52 across the trials were of similar magnitude. However, the difference between the two active treatment arms in Gonzales *et al*, 2006 was 5.5% (21.9% – 16.4%), which was slightly smaller than the 8.1% in Jorenby *et al*, 2006 (23%-14.9%). The pooled analysis showed that smokers who received varenicline were statistically significantly more likely to have remained abstinent from smoking from Week 9 to Week 52 than smokers who received bupropion with a RR of 1.4 (95% CI: 1.1, 1.8, p=0.002).

Varenicline versus NRT (Aubin *et al*, 2008)

In the Aubin *et al*, 2008 trial, the primary and secondary outcomes referred to continuous abstinence rate (CA) in the last 4 weeks of treatment. Analysis was done on the primary analysis population (all randomised and treated patients) and on the all randomised population. In the primary outcome, the last 4 weeks of treatment refers to weeks 8-11 in the NRT group and to weeks 9-12 in the varenicline group. The secondary outcome was measured for the last 4 weeks of treatment through week 52 (NRT: weeks 8-52; varenicline: weeks 9-52). Review of the results showed a higher response rate in smokers who received varenicline than in patients who received NRT in the last 4 weeks of treatment, i.e. between week 9 and week 12 (varenicline: 55.9% versus NRT: 43.2%; OR 1.70, 95% CI: 1.26-2.28). At week 52, the response rate in the varenicline group was higher than in the NRT group, i.e. 26.1% vs. 20.3% respectively (OR: 1.40, 95% CI: 0.99-1.99, p=0.056) but the difference was not statistically significant. Results mentioned above are from the primary analysis population. When analysis is performed on all randomised patients, the results are very similar but the difference at 52 weeks was statistically significant (varenicline: 25.9%; NRT: 19.8%; OR 1.44, 95% CI 1.02-2.03, p=0.040).

Table 6: Main benefit of varenicline in efficacy from Gonzales *et al*, 2006; Jorenby *et al*, 2006 and Aubin *et al*, 2008

Varenicline versus bupropion	***Varenicline***	***Bupropion***
Better response rate in varenicline than in bupropion for CQR (weeks 9-12)		
Gonzales *et al*, 2006	44.0%	29.5%
Jorenby *et al*, 2006	44.0%	29.8%
Better response rate in varenicline than in bupropion for CA (weeks 9-52)		
Gonzales *et al*, 2006	21.9%	16.4%
Jorenby *et al*, 2006	23.0%	14.9%
Smokers treated with varenicline were 1.5 more likely to have ceased smoking for the 4 weeks (weeks 9 to 12) than smokers treated with bupropion		
Gonzales *et al*, 2006	RR=1.49 (95% CI:1.22, 1.83)	
Jorenby *et al*, 2006	RR=1.47 (95% CI:1.20, 1.80)	
Pooled results	RR=1.50 (95% CI:1.30, 1.70)	
Smokers treated with varenicline were 1.3 to 1.5 more likely to have continued to refrain from smoking from week 9 to week 52 than smokers treated with bupropion		
Gonzales *et al*, 2006	RR=1.33 (95% CI:0.97, 1.82)	
Jorenby *et al*, 2006	RR=1.54 (95% CI:1.12, 2.12)	
Pooled results	RR=1.40 (95% CI:1.10, 1.80	
Lower rate of severe AE[1] in varenicline than in bupropion		
Gonzales *et al*, 2006	1.4%	1.5%
Jorenby *et al*, 2006	2.0%	2.4%
Varenicline versus NRT	***Varenicline***	**NRT**
Better response rate in varenicline (weeks 9-12) than in NRT (weeks 8-11) for CQR		
Aubin *et al*, 2008	55.9%	43.2%
Smokers treated with varenicline were 1.8 more likely to have ceased smoking for the 4 weeks (weeks 9-12) than smokers treated with NRT		
Aubin *et al*, 2008	RR=1.70 (95% CI:1.26, 2.28)	
Better response rate in varenicline (weeks 9-52) than in NRT (weeks 8-52) for CQR		
Aubin *et al*, 2008	26.1%	20.3%
Smokers treated with varenicline were 1.4 more likely to have continued to refrain from smoking from weeks 9 to 52 than smokers treated with NRT		
Aubin *et al*, 2008	RR=1.40 (95% CI:0.99, 1.99)	
Lower rate of severe AE in varenicline than in NRT		
Aubin *et al*, 2008	0.5%	2.2%

Abbreviations: CQR, continuous quite rate; CA, continuous abstinence; RR, relative risk; CI, confidence interval; AE, adverse event(s); NRT, nicotine replacement therapy.

1 Not including deaths

Adverse Events

Neuropsychiatric adverse events (Anthenelli *et al*, 2016)

One of the main objectives of Anthenelli *et al*, 2016 was to compare neuropsychiatric adverse events between smoking cessation treatments in patients with and without prespecified psychiatric diagnoses.

The overall incidence of the neuropsychiatric adverse event endpoint was similar across the four treatment groups: varenicline 4.0% (80 of 2016 participants), bupropion 4.5% (90 of 2006 participants), nicotine patch 3.9% (78 of 2022 participants), and placebo 3.7% (74 of 2014 participants). There were more neuropsychiatric adverse events in the psychiatric cohort (5.8%, 238 of 4074 participants) than the non-psychiatric cohort (2.1%, 84 of 3984 participants; p<0.0001 for the cohort effect; **Table 7**).

There was a treatment by cohort interaction (p=0.0652), so analyses of neuropsychiatric adverse events by treatment assignment are presented for each cohort separately. For the non-psychiatric cohort, the risk for the composite safety endpoint was lower for participants assigned to varenicline than those assigned to placebo (RD −1.28, 95% CI −2.40 to −0.15), although there was no significant difference in neuropsychiatric adverse events in those assigned to bupropion versus placebo (RD –0.08, –1.37 to 1.21). Differences between varenicline and nicotine patch and between bupropion and nicotine patch were also not significant in the nonpsychiatric cohort. In the psychiatric cohort, there were no significant pairwise treatment differences (95% Cis included zero).

Of the participants reporting the primary neuropsychiatric endpoint, the percentage of those reporting neuropsychiatric adverse events that were severe, met serious adverse event criteria, or led to treatment discontinuations or interventions (i.e., the clinically most significant events), was lower in the non-psychiatric cohort than the psychiatric cohort and was similar across treatment groups (**Table 7**).

Table 7: Summary of primary neuropsychiatric composite safety endpoint and its components (Anthenelli *et al*, 2016)

	Non-psychiatric cohort* (n=3984)				Psychiatric cohort* (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Primary composite neuropsychiatric endpoint	13 (1.3%)	22 (2.2%)	25 (2.5%)	24 (2.4%)	67 (6.5%)	68 (6.7%)	53 (5.2%)†	50 (4.9%)
Estimated primary composite neuropsychiatric adverse events (% [95% CI])	1.25% (0.60 to 1.90)	2.44% (1.52 to 3.36)	2.31% (1.37 to 3.25)	2.52% (1.58 to 3.46)	6.42% (4.91 to 7.93)	6.62% (5.09 to 8.15)	5.20% (3.84 to 6.56)	4.83% (3.51 to 6.16)
Difference in risk of composite primary endpoint (RD% [95% CI])								
Versus placebo	−1.28 (−2.40 to −0.15)	−0.08 (−1.37 to 1.21)	−0.21 (−1.54 to 1.12)	..	1.59 (−0.42 to 3.59)	1.78 (−0.24 to 3.81)	0.37 (−1.53 to 2.26)	..
Versus nicotine patch	−1.07 (−2.21 to 0.08)	0.13 (−1.19 to 1.45)	..	..	1.22 (−0.81 to 3.25)	1.42 (−0.63 to 3.46)	..	..
Versus bupropion	−1.19 (−2.30 to −0.09)	..	..	..	−0.20 (−2.34 to 1.95)	..	..	..
Components of primary neuropsychiatric composite endpoint								
Anxiety‡	0	1 (0.1%)	0	3 (0.3%)	5 (0.5%)	4 (0.4%)	6 (0.6%)	2 (0.2%)
Depression‡	1 (0.1%)	0	0	0	6 (0.6%)	4 (0.4%)	7 (0.7%)	6 (0.6%)
Feeling abnormal‡	0	0	0	0	0	1 (0.1%)	0	0
Hostility‡	0	1 (0.1%)	1 (0.1%)	0	0	0	0	0
Agitation§	10 (1.0%)	11 (1.1%)	19 (1.9%)	11 (1.1%)	25 (2.4%)	29 (2.9%)	21 (2.1%)	22 (2.2%)
Aggression§	3 (0.3%)	3 (0.3%)	2 (0.2%)	3 (0.3%)	14 (1.4%)	9 (0.9%)	7 (0.7%)	8 (0.8%)
Delusions§	0	0	1 (0.1%)	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
Hallucinations§	1 (0.1%)	0	0	0	5 (0.5%)	4 (0.4%)	2 (0.2%)	2 (0.2%)
Homicidal ideation§	0	0	1 (0.1%)	0	0	0	0	0
Mania§	0	1 (0.1%)	2 (0.2%)	2 (0.2%)	7 (0.7%)	9 (0.9%)	3 (0.3%)	6 (0.6%)
Panic§	0	4 (0.4%)	1 (0.1%)	3 (0.3%)	7 (0.7%)	16 (1.6%)	13 (1.3%)	7 (0.7%)
Paranoia§	0	1 (0.1%)	0	0	1 (0.1%)	0	0	2 (0.2%)
Psychosis§	0	0	1 (0.1%)	0	4 (0.4%)	2 (0.2%)	3 (0.3%)	1 (0.1%)

	Non-psychiatric cohort* (n=3984)				Psychiatric cohort* (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Suicidal behaviour§	0	1 (1.0%)	1 (0.1%)	0	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Suicidal ideation§	0	1 (0.1%)	2 (0.2%)	3 (0.3%)	5 (0.5%)	2 (0.2%)	3 (0.3%)†	2 (0.2%)
Completed suicide§	0	0	0	1 (0.1%)	0	0	0	0
Primary composite neuropsychiatric endpoint (severe intensity only)	1 (0.1%)	4 (0.4%)	3 (0.3%)	5 (0.5%)	14 (1.4%)	14 (1.4%)	14 (1.4%)	13 (1.3%)
Components of primary neuropsychiatric composite endpoint (severe intensity only)								
Anxiety‡	0	1 (0.1%)	0	3 (0.3%)	5 (0.5%)	4 (0.4%)	6 (0.6%)	2 (0.2%)
Depression‡	1 (0.1%)	0	0	0	6 (0.6%)	4 (0.4%)	7 (0.7%)	6 (0.6%)
Feeling abnormal‡	0	0	0	0	0	1 (0.1%)	0	0
Hostility‡	0	1 (0.1%)	1 (0.1%)	0	0	0	0	0
Agitation‡	0	0	2 (0.2%)	0	1 (0.1%)	1 (0.1%)	4 (0.4%)	2 (0.2%)
Aggression‡	1 (1.0%)	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Delusions‡	0	0	0	0	0	0	0	0
Hallucinations‡	0	0	0	0	0	1 (0.1%)	0	0
Homicidal ideation‡	0	0	0	0	0	0	0	0
Mania‡	0	0	0	0	2 (0.2%)	1 (0.1%)	0	0
Panic‡	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Paranoia‡	0	0	0	0	0	0	0	0
Psychosis‡	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0
Suicidal behaviour‡	0	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Suicidal ideation‡	0	0	0	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	0
Completed suicide‡	0	0	0	1 (0.1%)	0	0	0	0
Events in the primary endpoint								
Serious adverse events¶	0	1 (0.1%)	2 (0.2%)	3 (0.3%)	6 (0.6%)	5 (0.5%)	3 (0.3%)†	3 (0.3%)
Resulting in permanent treatment discontinuations	1 (0.1%)	5 (0.5%)	7 (0.7%)	3 (0.3%)	16 (1.6%)	15 (1.5%)	12 (1.2%)	15 (1.5%)

	Non-psychiatric cohort* (n=3984)				Psychiatric cohort* (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Leading to interventions**	0	2 (0.2%)	1 (0.1%)	3 (0.3%)	7 (0.7%)	12 (1.2%)	7 (0.7%)	11 (1.1%)
Combined serious adverse events, severe adverse events, and leading to treatment discontinuations or interventions (at least one of)	2 (0.2%)	8 (0.8%)	8 (0.8%)	10 (1.0%)	28 (2.7%)	28 (2.8%)	21 (2.1%)†	29 (2.9%)

Data are n (%), unless otherwise stated. Based on least squares means analysis, point estimate, and its 95% CI. Estimated risk difference is based on a General Linear Model with terms treatment, cohort, region, and treatment by cohort interaction. Region uses two-level classification (USA, non-USA). Adverse events reported during treatment and 30 days or less after last dose. Participants are counted only once per each row, even if they have reported multiple events; participants can be counted in multiple rows. RD=risk difference.

**All-treated population. †One additional participant in the nicotine patch group (psychiatric cohort) who reported moderate suicidal ideation (serious adverse events) was identified after the clinical database was locked; consequently, the participant was not included in the analysis of the primary study endpoint. ‡Severe intensity adverse events. §Moderate and severe intensity adverse event. ¶Serious adverse events were: non-psychiatric cohort: bupropion, suicide attempt (1); nicotine patch, suicide attempt (1), panic (1); placebo, suicidal ideation (2), completed suicide (1); psychiatric cohort: varenicline, suicidal ideation (2), depression (1), auditory hallucination (1), exacerbation of bipolar I disorder (1), anxiety plus self-injurious behaviour (1); bupropion, suicide attempt plus schizoaffective disorder (1), exacerbations of bipolar I disorder (2) and bipolar II disorder (1), emotional disorder plus neuropsychiatric symptoms (1); nicotine patch, anxiety (2), depression (1); placebo, suicide attempt (1), suicidal ideation (1), aggression (1). **Interventions include: psychotropic medication, psychotherapy, counselling, and admission to hospital.*

Source: Anthenelli et al, 2016 Table 2

The number of participants reporting suicidal ideation or behaviour on the Columbia-Suicide Severity Rating Scale (C-SSRS) was greater in the psychiatric cohort than in the non-psychiatric cohort and similar across treatment groups (**Table 8**). There was one completed suicide in the study in a placebo-treated participant in the non-psychiatric cohort.

Table 8: Columbia-Suicide Severity Rating Scale (C-SSRS)

	Non-psychiatric cohort* (n=3984)				Psychiatric cohort* (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
During treatment and ≤30 days after last dose								
Assessed	988	983	996	995	1017	1012	1006	1006
Suicidal behavior and/or ideation	7 (1%)	4 (<1%)	3 (<1%)	7 (1%)	27 (3%)	15 (1%)	20 (2%	25 (2%)
Suicidal behaviour†‡	0	0	1 (<1%)	1 (<1%)§	0	1 (<1%)	0	2 (<1%)
Suicidal ideation	7 (1%)	4 (<1%)	3 (<1%)	6 (1%)	27 (3%)	15 (1%)	20 (2%)	25 (2%)
During treatment and ≤30 days after last dose								
Assessed	807	816	800	805	833	836	824	791
Suicidal behavior and/or ideation	3 (<1%)	2 (<1%)	3 (<1%)	4 (<1%)	14 (2%)	4 (<1%)	9 (1%)	11 (1%)
Suicidal behaviour†¶	0	1 (<1%)	0	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Suicidal ideation	3 (<1%)	2 (<1%)	3 (<1%)	4 (<1%)	14 (2%)	4 (<1%)	9 (1%)	11 (1%)

Data are n or n (%).

**All-treated population. †Suicidal behaviour (most severe for each participant with positive answers on the C-SSRS). ‡During treatment: non-psychiatric cohort: nicotine patch, suicide attempt (1); placebo, completed suicide (1); psychiatric cohort: bupropion, suicide attempt (1); placebo, suicide attempt (2). §Completed suicide. ¶During follow-up: non-psychiatric cohort: bupropion, suicide attempt (1); psychiatric cohort: varenicline, suicide attempt (1); nicotine patch, aborted attempt (1); placebo, aborted attempt (1).*

Source: Anthenelli et al, 2016 Table 3

The average total Hospital Anxiety and Depression Scale (HADS) score improved from baseline through the treatment phase by about 2 points in the non-psychiatric cohort and 3 points in the psychiatric cohort, an effect that was similar across the treatment groups.

Table 9 lists all adverse events (mild, moderate, and severe) in the Psychiatric Disorder MedDRA category occurring in at least 1% of any treatment group in either cohort, irrespective of whether they met the criteria for the primary neuropsychiatric adverse event endpoint. Those in the psychiatric cohort were more likely to report neuropsychiatric adverse events of all types than those in the non-psychiatric cohort. The profile of adverse events exhibited (e.g., abnormal dreams more common for varenicline and nicotine patch compared with placebo) was consistent with previous reports.

Table 9: Mild, moderate, or severe adverse events* coding to the MedDRA category psychiatric disorders reported by at least 1% of participants in any treatment group

	Non-psychiatric cohort† (n=3984)				Psychiatric cohort† (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Psychiatric disorders	315 (32%)	332 (34%)	301 (30%)	259 (26%)	405 (39%)	435 (43%)	420 (41%)	354 (35%)
Abnormal dreams	83 (8%)	47 (5%)	111 (11%)	39 (4%)	118 (12%)	84 (8%)	140 (14%)	53 (5%)
Agitation	32 (3%)	29 (3%)	28 (3%)	25 (3%)	47 (5%)	56 (6%)	39 (4%)	41 (4%)
Anger	3 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	11 (1%)	4 (<1%)	4 (<1%)	5 (<1%)
Anxiety‡	46 (5%)	64 (6%)	45 (4%)	57 (6%)	86 (8%)	105 (10%)	93 (9%)	63 (6%)
Depressed mood	31 (3%)	13 (1%)	27 (3%)	29 (3%)	47 (5%)	47 (5%)	52 (5%)	52 (5%)
Depression	17 (2%)	13 (1%)	8 (1%)	15 (2%)	49 (5%)	45 (4%)	47 (5%)	46 (5%)
Depressive symptom	5 (1%)	3 (<1%)	2 (<1%)	2 (<1%)	11 (1%)	8 (1%)	12 (1%)	13 (1%)
Initial insomnia	7 (1%)	6 (1%)	10 (1%)	4 (<1%)	15 (1%)	8 (1%)	10 (1%)	2 (<1%)
Insomnia	95 (10%)	126 (13%)	91 (9%)	73 (7%)	94 (9%)	119 (12%)	104 (10%)	66 (7%)
Irritability	34 (3%)	29 (3%)	47 (5%)	37 (4%)	48 (5%)	42 (4%)	61 (6%)	67 (7%)
Major depression	3 (<1%)	0	1 (<1%)	3 (<1%)	7 (1%)	10 (1%)	4 (<1%)	2 (<1%)
Middle insomnia	7 (1%)	15 (2%)	13 (1%)	6 (1%)	11 (1%)	16 (2%)	13 (1%)	8 (1%)
Nervousness	14 (1%)	18 (2%)	11 (1%)	9 (1%)	21 (2%)	19 (2%)	17 (2%)	27 (3%)
Nightmare	9 (1%)	7 (1%)	26 (3%)	3 (<1%)	13 (1%)	9 (1%)	30 (3%)	14 (1%)
Panic attack	2 (<1%)	7 (1%)	2 (<1%)	3 (<1%)	9 (1%)	19 (2%)	13 (1%)	11 (1%)
Restlessness	14 (1%)	14 (1%)	15 (1%)	14 (1%)	17 (2%)	20 (2%)	14 (1%)	9 (1%)
Sleep disorder	31 (3%)	37 (4%)	17 (2%)	19 (2%)	34 (3%)	36 (4%)	28 (3%)	23 (2%)
Tension	2 (<1%)	10 (1%)	2 (<1%)	2 (<1%)	9 (1%)	5 (<1%)	10 (1%)	6 (1%)

Data are n (%).

**As classified by the Medical Dictionary for Regulatory Activities (MedDRA, version 18.0) in the System Organ Class category of psychiatric disorders and derived preferred terms and occurring during treatment and at most 30 days after last dose. †All-treated population. ‡As per MedDRA (version 18.0) preferred term Anxiety; this differs from the Anxiety component of the primary composite endpoint, which is a cluster of several MedDRA (version 18.0) preferred terms related to anxiety disorders; the same note applies to other preferred terms in this table (e.g., depression, agitation).*

Source: Anthenelli et al, 2016 Table 3

Overall adverse events

Anthenelli et al 2016

Incidences of general adverse events, serious adverse events, deaths, treatment discontinuations, and adverse events observed in at least 5% of participants are summarised in the appendix. Overall, the treatments were well tolerated. In brief, across cohorts, the most frequent adverse events by treatment group were nausea (varenicline, 25% [511 of 2016 participants]), insomnia (bupropion, 12% [245 of 2006 participants]), abnormal dreams (nicotine patch, 12% [251 of 2022 participants]), and headache (placebo, 10% [199 of 2014 participants]) (**Table 10**).

Table 10: Summary of general adverse events* (Anthenelli *et al*, 2016)

	Non-psychiatric cohort* (n=3984)				Psychiatric cohort* (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Any adverse event	720 (72.7%	704 (71.2%)	698 (69.4%)	649 (65.0%)	783 (76.3%)	742 (73.0%)	737 (72.5%)	696 (68.6%)
Serious adverse events‡	16 (1.6%)	19 (1.9%)	21 (2.1%)	16 (1.6%)	23 (2.2%)	29 (2.9%)	24 (2.4%)	25 (2.5%)
Adverse events resulting in permanent treatment discontinuation	57 (5.8%)	75 (7.6%)	74 (7.4%)	29 (2.9%)	109 (10.6%)	101 (9.9%)	88 (8.7%)	93 (9.2%)
Deaths §	0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)
Most common adverse events (≥5%)¶								
Gastrointestinal signs and symptoms								
Nausea	243 (24.5%)	90 (9.1%)	95 (9.4%)	63 (6.3%)	268 (26.1%)	111 (10.9%)	104 (10.2%)	74 (7.3%)
Salivary gland condition								
Dry mouth	29 (2.9%)	70 (7.1%)	31 (3.1%)	26 (2.6%)	37 (3.6%)	76 (7.5%)	28 (2.8%)	38 (3.7%)
Administration-site reactions								
Application-site pruritus	11 (1.1%)	6 (0.6%)	51 (5.1%)	11 (1.1%)	11 (1.1%)	6 (0.6%)	58 (5.7%)	5 (0.5%)
General system disorders not elsewhere classified								
Fatigue	39 (3.9%)	20 (2.0%)	28 (2.8%)	24 (2.4%)	85 (8.3%)	37 (3.6%)	47 (4.6%)	59 (5.8%)
Infections – pathogens unspecified								
Nasopharyngitis	86 (8.7%)	79 (8.0%)	65 (6.5%)	73 (7.3%)	88 (8.6%)	77 (7.6%)	61 (6.0%)	62 (6.1%)
Upper respiratory tract infection	47 (4.7%)	48 (4.9%)	40 (4.0%)	55 (5.5%)	62 (6.0%)	56 (5.5%)	57 (56.%)	60 (5.9%)
Headache								
Headache	116 (11.7%)	87 (8.8%)	129 (12.8%)	95 (9.5%)	129 (12.6%)	99 (9.7%)	104 (10.2%)	104 (10.2%)
Neurological disorders not elsewhere classified								
Dizziness	33 (3.3%)	51 (5.2%)	38 (3.8%)	28 (2.8%)	45 (4.4%)	47 (4.6%)	47 (4.6%)	38 (3.7%)
Anxiety disorders and symptoms								
Agitation	32 (3.2%)	29 (2.9%)	28 (2.8%)	25 (2.5%)	47 (4.6%)	56 (5.5%)	39 (3.8%)	41 (4.0%)
Anxiety	46 (4.6%)	64 (6.5%)	45 (4.5%)	57 (5.7%)	86 (8.4%)	105 (10.3%)	93 (9.2%)	63 (6.2%)
Depressed mood disorders and disturbances								

	Non-psychiatric cohort* (n=3984)				Psychiatric cohort* (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Depressed mood	31 (3.1%)	13 (1.3%)	27 (2.7%)	29 (2.9%)	47 (4.6%)	47 (4.6%)	52 (5.1%)	52 (5.1%)
Mood disorders and disturbances not elsewhere classified								
Irritability	34 (3.4%)	29 (2.9%)	47 (4.7%)	37 (3.7%)	48 (4.7%)	42 (4.1%)	61 (6.0%)	67 (6.6%)
Sleep disorders and disturbances								
Abnormal dreams	83 (8.4%)	47 (4.8%)	111 (11.0%)	39 (3.9%)	118 (11.5%)	84 (8.3%)	140 (13.8%)	53 (5.2%)
Insomnia	95 (9.6%)	126 (12.7%)	91 (9.0%)	73 (7.3%)	94 (9.2%)	119 (11.7%)	104 (10.2%)	66 (6.5%)

Data are n (%).

**Adverse events reported during treatment and ≤30 days after last dose. †All-treated population. ‡Serious adverse events that met the US FDA definition of life-threatening, resulting in death, hospitalisation, disability or permanent damage, congenital anomaly or birth defect. §The deaths were: varenicline (0); bupropion (2) – heroin overdose (non-psychiatric cohort), cardiovascular event (psychiatric cohort); placebo (2) – completed suicide (non-psychiatric cohort), pulmonary embolism (psychiatric cohort). In addition, the deaths that occurred >30 days after the last study treatment dose and not included in the table were: varenicline (0); bupropion (1) – lung cancer (psychiatric cohort); nicotine patch (3) – prostate cancer (non-psychiatric cohort), oesophageal adenoma (psychiatric cohort), sepsis after randomisation, unknown if nicotine replacement therapy was taken (psychiatric cohort); placebo (2) – road traffic accident (non-psychiatric cohort), myocardial infarction (non-psychiatric cohort). ¶Classified by the Medical Dictionary for Regulatory Activities (MedDRA, v18.0) symptom categories (System Organ Class) and derived preferred terms.*

Gonzales et al, 2006, Jorenby et al, 2006 and Aubin et al, 2008

Varenicline's most reported adverse events (AEs) in the three head to head RCTs (Gonzales *et al*, 2006, Jorenby *et al*, 2006 and Aubin *et al*, 2008) were nausea, insomnia, abnormal dreams and headache. Incidence of all adverse events reported by 5% or more of smokers treated with varenicline is presented in **Table 11**.

Table 11: Nature and incidence of adverse events reported by ≥ 5% of either varenicline treatment group

Adverse Events	Gonzales *et al*, 2006	Jorenby *et al*, 2006	Aubin *et al*, 2008
Nausea	28.1	29.4	37.2
Insomnia	14.0	14.3	21.3
Headache	15.5	12.8	19.1
Abnormal dreams	10.3	13.1	11.7
Dry mouth	6.6	5.5	N/A
Irritability	6.0	0.6	N/A
Dizziness	6.0	6.4	7.4
Flatulence	5.7	5.8	5.9
Sleep disorder	5.7	4.7	N/A
Nasopharyngitis	5.7	5.0	N/A
Constipation	5.4	9.0	8.2
Disturbance in attention	4.9	2.9	6.4
Dyspepsia	4.3	5.5	N/A
Vomiting	3.7	5.2	6.1
Dysgeusia	3.7	4.1	5.9
Fatigue	3.7	7.3	5.6
Abdominal pain (upper)	2.6	0.9	5.6

Abbreviations: N/A, not applicable

Safety results from the three trials showed that varenicline, when compared to bupropion, placebo or NRT, is associated with a higher rate of abnormal dreams, headache and nausea. As it relates to insomnia, varenicline is associated with a lower rate than bupropion and a slightly higher rate than placebo and NRT. Details are reported in **Table 12**.

Table 12: Summary of individual adverse events reported by ≥ 10% smokers treated with varenicline

Study/Treatment	Adverse Event			
	Nausea (%)	Insomnia (%)	Abnormal dreams (%)	Headache (%)
Gonzales *et al*, 2006				
Varenicline	28.1	14.0	10.3	15.5
Bupropion	12.5	21.9	5.5	14.3
Placebo	8.4	12.8	5.5	12.2
Jorenby *et al*, 2006				
Varenicline	29.4	14.3	13.1	12.8

Study/Treatment	Adverse Event			
	Nausea (%)	Insomnia (%)	Abnormal dreams (%)	Headache (%)
Bupropion	7.4	21.2	5.9	7.9
Placebo	9.7	12.4	3.5	12.6
Aubin *et al*, 2008				
Varenicline	37.2	21.3	11.7	19.1
NRT	9.7	19.2	8.4	9.7

Nausea is clearly the most reported adverse events when taking varenicline. The consumer medicine information (CMI) leaflet informs the consumer on how to manage nausea caused by varenicline. In clinical trials, nausea usually occurred in the first week of taking varenicline. Despite nausea, the majority of smokers were able to continue their treatment with varenicline. Among patients reporting nausea, some found it helpful to take varenicline with food.

Overall, the treatments are associated with different side effects. Therefore, it is difficult to make any strong conclusions about their tolerability compared to one another based purely on the rates of these AE alone. Therefore, it is important to consider the relative impact of these events. The most valid way to assess this is to consider the rates of discontinuations versus the rates of treatment-related AEs. As shown in **Table 13**, the total number of subjects that experienced AEs was similar across the three treatment arms for both Gonzales *et al*, 2006 and Jorenby *et al*, 2006 trials and similar across the two treatment arms for the Aubin *et al*, 2008 trial.

Table 13: Overview of adverse events

	Gonzales *et al*, 2006			Jorenby *et al*, 2006			Aubin *et al*, 2008	
	Varenicline (n=349)	Bupropion (n=329)	Placebo (n=344)	Varenicline (n=343)	Bupropion (n=340)	Placebo (n=340)	Varenicline (n=376)	NRT (n=370)
Parameter	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
All AE	275 (78.8)	258 (78.4)	257 (74.7)	273 (79.6)	262 (77.1)	258 (75.9)	319 (84.8)	260 (70.3)
Treatment related to AE	241 (69.1)	202 (61.4)	183 (53.2)	232 (67.6)	209 (61.5)	188 (55.3)	N/A	N/A
Treatment discontinuation due to AE	30 (8.6)	50 (15.2)	31 (9.0)	36 (10.5)	43 (12.6)	25 (7.4)	30 (8.0)	16 (4.3)
Dose reduction or temporary discontinuation due to AE	16 (4.6)	11 (3.3)	14 (4.1)	4 (1.2)	14 (4.1)	9 (2.6)	44 (11.7)	25 (6.8)
Deaths	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Severe AE[1]	5 (1.4)	5 (1.5)	8 (2.3)	7 (2.0)	8 (2.4)	6 (1.8)	2 (0.5)	8 (2.2)

Abbreviations: AE, adverse event(s)

[1] *Not including deaths*

Considering the data presented in **Table 11**, **Table 12** and **Table 13**, it is clear that varenicline is associated with a lower rate of insomnia and a lower rate of treatment discontinuation due to AEs when compared to bupropion. Varenicline is also associated with slightly lower rate of severe AEs when compared to bupropion and NRT. Details are presented in **Table 14**.

Table 14: Main benefits in safety for varenicline compared to bupropion and nicotine replacement therapy

Varenicline versus bupropion	**Varenicline**	**Bupropion**
Lower rate of insomnia in varenicline versus bupropion:		
Gonzales *et al*, 2006	14.0%	21.9%
Jorenby *et al*, 2006	14.3%	21.2%
Lower treatment discontinuation due to AE in varenicline versus bupropion:		
Gonzales *et al*, 2006	8.6%	15.2%
Jorenby *et al*, 2006	10.5%	12.6%
Lower rate of severe AE in varenicline versus bupropion		
Gonzales *et al*, 2006	1.4%	1.5%
Jorenby *et al*, 2006	2.0%	2.4%
Varenicline versus NRT	**Varenicline**	**NRT**
Lower rate of severe AE in varenicline versus NRT		
Aubin *et al*, 2008	0.5%	2.2%

Abbreviations: AE, adverse event(s); NRT, nicotine replacement therapy.

3.2.2 Other clinical evidence

A summary of other clinical evidence is included in **Table 15**.

Forty-six publications were identified which included forty studies. Of the remaining six publications: three publications were subgroups of EAGLES (Ayers *et al*, 2020, Evins *et al*, 2019 and Heffner *et al*, 2019); Smith *et al* (2013) and Carson *et al* (2014) reported on the same study at different timepoints; Nakamura *et al* (2017) reported on a subgroup of Ebbert *et al* (2015). Finally, Tashkin *et al* (2011a) and Tashkin *et al* (2011b) reported on different endpoints of the same study.

Of the forty studies: twenty-six were randomised controlled trials (RCTs) and three were open-label studies, two of which were comparative (one with NRT [Baker *et al*, 2016] and the other with counselling [Carson *et al*, 2014]) and one was noncomparative (Price *et al*, 2016). Twenty-four of the RCTs were placebo-controlled. Of the remaining two, Schnoll *et al* (2019) compared 12-weeks of varenicline + 12 weeks of placebo to twenty-four weeks of varenicline and Tulloch *et al* (2016) compared varenicline to NRT.

Benli *et al* (2017) was categorised as a prospective comparative study (vs bupropion). Chang *et al* (2017), Jiménez-Ruiz *et al* (2017), Politis *et al* (2018), Taylor *et al* (2017) and Taylor *et al* (2020) were described as prospective cohort studies. NRT was the comparator in Chang *et al*, (2017), Taylor *et al* (2017), Taylor *et al* (2020), Jiménez-Ruiz *et al* (2017) and Politis *et al*, 2018 were non-comparative. Carney *et al* (2019), Chang *et al* (2019), Itani *et al* (2019), Jiménez-Ruiz *et al* (2018) and Kotz *et al* (2017) were retrospective cohort studies. Carney *et*

al (2019) included both NRT and bupropion as comparators while Chang *et al* (2019), Itani *et al* (2019), Jiménez-Ruiz *et al* (2018) and Kotz *et al* (2017) included NRT as the comparator.

Populations included alcohol-dependent smokers (Zawertalio *et al*, 2020); asthmatic smokers (Westergaard *et al*, 2015); smokers with stable cardiovascular disease (Rigotti *et al*, 2010); Asian smokers (Nakamura *et al*, 2007; Wang *et al*); smokers attending GP practice (Taylor *et al*, 2017); smokers living with HIV (Ashare *et al*, 2019; Mercie *et al*, 2018); smokers with cancer (Price *et al*, 2016; Schnoll *et al*, 2019); smokers with COPD (Jiménez-Ruiz *et al*, 2017; Kotz *et al*, 2017; Le Mao *et al*, 2020; Politis *et al*, 2018; Tashkin *et al*, 2011a); smokers with neurodevelopmental disorders (Itani *et al*, 2019); smokers with mental health disorders (Anthenelli *et al*, 2013; Chengappa *et al*, 2014; Evins *et al* , 2014; Jiménez-Ruiz *et al*, 2018; Taylor *et al*, 2020; Williams *et al*, 2012); hospitalised patients (Carney *et al*, 2019; Carson *et al*, 2014; Chang *et al*, 2019; Eisenberg *et al*, 2016; Steinberg *et al*, 2011); smokers scheduled for surgery (Wong *et al*, 2012) and smokers enrolled in smoking cessation programs (Baker et al, 2016; Benli *et al*, 2017; Chang *et al*, 2017; Cinciripini *et al*, 2013). Tuisku *et al* (2016) included young adult smokers and Ebbert *et al* (2016) included light smokers.

Gonzales *et al* (2014) compared varenicline to bupropion and placebo in relapsed smokers who had abstained for less than 3 months in the previous year. Rennard *et al* (2012) allowed flexible quit dates and compared varenicline to placebo. Tulloch *et al* (2016) compared NRT, NRT patches in combination with gum or inhaler and varenicline. Tonstad *et al* (2006) compared varenicline with placebo for 12 weeks in subjects who had quit with 12 weeks of varenicline. Ebbert *et al* (2015) was performed in cigarette smokers not willing or able to quit within the next month but willing to reduce cigarette consumption and make a quit attempt at 3 months. Bohadana *et al* (2020) employed a 6-week preloading regime with varenicline.

The majority of comparative studies demonstrated superiority of varenicline to comparators for 7-day point prevalence of abstinence and continuous abstinence and non-comparative studies showed a favourable outcome with varenicline.

In Ashare *et al* (2019) continuous abstinence from Week 9 to 12 was higher for varenicline vs. placebo, however, at Week 24, there was no effect of varenicline for point prevalence, continuous abstinence or time to relapse. In Baker *et al* (2016) there were no differences in outcomes between nicotine patches, nicotine patches and lozenges of inhalers and varenicline. Chang (2017) demonstrated superiority of varenicline in smokers aged 25-54 years, however for smokers aged 55 years or older, varenicline and NRT had equivalent effectiveness.

In terms of adverse events, findings were similar to the pivotal studies.

Table 15: Summary of other clinical evidence

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
Anthenelli *et al*, 2013	Phase 4, MC, PG, 1:1 allocation, DB, rand trial [12 wks and 40-wk non-treatment follow-up]	Varenicline 1 mg BD (after uptitration) (N = 256) Placebo (N = 296)	525 adult smokers with stably treated current or past major depression and no recent cardiovascular events	Primary outcome was CO–confirmed CAR for weeks 9 to 12. Other outcomes included CARs assessed during non-treatment follow-up and ratings of mood, anxiety, and suicidal ideation or behaviour.	Varenicline-treated participants had higher CARs versus placebo at weeks 9 to 12 (35.9% vs. 15.6%; OR, 3.35 [95% CI, 2.16 to 5.21]; *P* <0.001), 9 to 24 (25.0% vs. 12.3%; OR, 2.53 [CI, 1.56 to 4.10]; *P* < 0.001), and 9 to 52 (20.3% vs. 10.4%; OR, 2.36 [CI, 1.40 to 3.98]; *P* = 0.001). No clinically relevant differences between groups in suicidal ideation or behavior and no overall worsening of depression or anxiety in either group. Most frequent AE was nausea (varenicline, 27.0%; placebo, 10.4%). Two varenicline-group participants died during the nontreatment phase.
Ashare *et al*, 2019	Phase three, SC, rand, PC, DB [12 weeks treatment and further 12 weeks non-treatment follow-up]	Varenicline 1 mg BD (after uptitration) (N = 89) Placebo (N = 90)	179 PLWH on ART	Primary outcome was 7PP of abstinence (CO-confirmed) at Weeks 12 and 24. Secondary outcomes included CAR and time to relapse. Safety measures were treatment-related side effects, AEs, blood pressure, viral load, and ART adherence.	Continuous abstinence from Week 9 to 12 was higher for varenicline vs. placebo (23.6% vs. 10%; OR = 4.65, 95% CI:1.71−12.67, P = .003); at Week 24, there was no effect of varenicline for point prevalence (14.6% vs. 10%), continuous abstinence (10.1% vs. 6.7%), or time to relapse (Ps > .05). There were no differences between varenicline and placebo on safety measures (Ps > .05).
Ayers *et al*, 2020 (subgroup analysis of Anthenelli *et al*, 2016)	Rand, DP, triple-dummy, PC and active-controlled [12 weeks treatment and further 12 weeks non-treatment follow-up]	Nicotine patch; 21 mg per day with taper Varenicline 1 mg BD Bupropion 150 mg BD	Post hoc analyses in 712 smokers with AD (posttraumatic stress disorder [PTSD], n = 192; generalised anxiety disorder [GAD], n = 243; panic disorder [PD], n = 277) and in a nonpsychiatric cohort (NPC; n = 4,028). P	Composite measure based on post-marketing reports of neuropsychiatric adverse events in smokers taking varenicline and bupropion CAR for Weeks 9-12 CAR for Weeks 9-24 7 Day point prevalence of abstinence Other safety	Varenicline demonstrated superior efficacy to placebo in smokers with GAD and PD, respectively (OR = 4.53; 95% confidence interval [CI] = 1.20–17.10; and OR = 8.49; 95% CI = 1.57–45.78); NRT was superior to placebo in smokers with PD (OR = 7.42; 95% CI = 1.37–40.35). While there was no statistically significant effect of any treatment on CAR 9–12 for smokers with PTSD, varenicline improved 7PP abstinence at end of treatment in this subcohort. NPSAE incidence for PTSD (6.9%), GAD (5.4%), and PD (6.2%) was higher versus NPC (2.1%), regardless of treatment.
Baker *et al*, 2016	Three-group, OL, rand, ITT clinical trial in smokers recruited in Madison, Wisconsin, and Milwaukee, Wisconsin, communities	Nicotine patches: 21 mg daily for 8 weeks then 14 mg daily for 2 weeks then 7 mg daily for 2 weeks. Smokers who smoked 5-10 cigarettes per day received 10 weeks of 14 mg patches, then 2 weeks of 7 mg patches (N = 241)	Participants recruited via 2 sources: (1) contacting participants in an ongoing longitudinal study of smokers, the Wisconsin Smokers Health Study, and (2) via media and community outreach.	Primary outcome was CO–confirmed self-reported 7PP of abstinence at 26 weeks. Secondary outcomes were CO–confirmed self-reported initial abstinence, prolonged abstinence at 26 weeks, and point-prevalence abstinence at weeks 4, 12, and 52.	Treatments did not differ on any abstinence outcome measure at 26 or 52 weeks, including 7PP of abstinence at 26 weeks (nicotine patch, 22.8% [55/241]; varenicline, 23.6% [100/424]; and C-NRT, 26.8% [113/421]) or at 52 weeks (nicotine patch, 20.8% [50/241]; varenicline, 19.1% [81/424]; and C-NRT, 20.2% [85/421]). At 26 weeks, risk differences for abstinence were, for patch vs varenicline, −0.76% (95% CI, −7.4% to 5.9%); for patch vs

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
	[12 wks treatment and 40 wks follow up]	Varenicline: Pre-quit regimen was 0.5 mg once daily for 3 days then 0.5 BD for 4 days then 1 mg BD for 3 days. From TQD: 1 mg twice daily for 11 weeks. (N = 424) Nicotine patch and lozenges (C-NRT): Nicotine patch as above plus 5 x 2-mg or 4-mg nicotine lozenges (based on morning smoking latency) (N = 421) Six counselling sessions were offered			C-NRT, −4.0% (95% CI, −10.8% to 2.8%); and for varenicline vs C-NRT, −3.3% (95% CI, −9.1% to 2.6%). All medications were well tolerated, but varenicline produced more frequent AEs than did the nicotine patch for vivid dreams, insomnia, nausea, constipation, sleepiness, and indigestion.
Benli *et al*, 2017	Prospective, comparative study [evaluated at 15 days then up to 12 months after smoking cessation]	Varenicline Bupropion	Individuals over 18 years included in smoking cessation program (N=405)	Level of CO < 5 ppm and 7PP of abstinence	The rates of success in the 1st and 2nd weeks, and 1st, 3rd and 6th months were significantly higher in the varenicline group than in the bupropion group ($p < 0.05$). At the end of one year, the rate of smoking cessation was determined as 13.9% (n = 34) in the varenicline group and 6.2% (n = 10) in the bupropion group. The difference was statistically significant ($p = 0.015$). At the end of 1 year when the previous 7 days smoking status was evaluated with the 'point prevalence abstinence' measurement as the success criteria, success rates were 20.5% with varenicline and 18.6% with bupropion and the difference was not significant ($p = 0.646$). The individuals who used the medications for 45 days or longer were more successful in smoking cessation ($p < 0.001$). The most common reason given for discontinuing the medication was side-effects (31.5%). No significant difference was determined between the groups in respect of side-effects observed.
Bohadana *et al*, 2020	DB, rand, SC	Varenicline Placebo <u>Extended preloading group:</u> Varenicline 0.5 mg daily for 3 days then 0.5 mg twice daily for 4 days then varenicline 1 mg twice daily for 5 weeks before TQD then varenicline for 12 weeks (N=121) <u>Standard preloading:</u> Placebo for 5 weeks followed by varenicline 0.5 mg daily for 3 days then 0.5 mg twice daily for 4 days (N=121)	Daily smokers ≥18 years old, who smoked ≥ 10 cigarettes/day, had smoked ≥5 pack-years, had a carbon monoxide (CO) level in expired air of ≥10 parts per million (ppm), and were willing to stop smoking.	Primary outcome was 24-week biochemically verified CAR from weeks 6 (TQD) Secondary outcomes included 23-week CAR from 1-week post-TQD (week 7) to week 30, and the 7PP abstinence at week 30. Other measures included pre- and post-quit rewards, smoking urges, nausea, aversion, and markers of cigarette consumption.	24-week CAR, weeks 6-30 with extended preloading was significantly higher than with standard preloading (23.1% vs. 4.1%; risk reduction [RR]: -0.19 [95% confidence interval [CI]:-0.10—0.24]; $p < 0.001$). Extended preloading also showed better secondary outcomes. Extended preloading significantly decreased pre-quit rewards, urges, and smoke intake, including unsolicited smoking abstinence. Post-quit urges remained remarkably lower with extended preloading. Participants receiving extended preloading reported more nausea at week 4 (39.6% vs 11.5%) and abnormal dreams at week 6 (7.7% vs. 0%). Participants receiving standard preloading reported more constipation at week 7 (7.6% vs. 0%) and dizziness at weeks 7 (12.1% vs. 2.5%) and 12 (10.7% vs 1.4%)

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
		then varenicline 1 mg twice daily for 12 weeks (N=121)			
Carney *et al*, 2019	Retrospective new-user cohort	Varenicline Bupropion NRT	Adults aged 18 or older who initiated varenicline, bupropion 150 mg sustained release (SR) or any form of nicotine replacement therapy. Limited to patients with no diagnosis or treatment for depression (N=618,497)	The primary outcome was a composite of hospitalised CV events. Secondary outcomes included a composite of hospitalised neuropsychiatric events and individual components of the primary outcome	Compared with NRT (n = 32 237), varenicline (n = 454 698) was associated with a 20% lower 1-year CV risk [adjusted relative risk (RR) = 0.80, 95% confidence interval (CI) = 0.75– 0.85], and bupropion (n = 131 562) was associated with a 25% lower 1-year CV risk (RR = 0.75, 95% CI = 0.69–0.81). Varenicline was associated with a 35% lower 1-year risk of neuropsychiatric hospitalisation versus NRT (RR = 0.65, 95% CI = 0.59–0.72), and bupropion was associated with a 21% increase in 1-year risk of neuropsychiatric hospitalisation (RR = 1.21, 95% CI = 1.09–1.35).
Carson *et al*, 2014 Smith *et al*, 2013	OL, rand, MC controlled clinical trial [12-wks treatment and 40 wks follow up]	Varenicline started during hospital admission: 0.5 mg/day for 3 days, 0.5 mg BD for 4 days, then 1 mg BD + Quitline counselling (N = 196) vs Quitline counselling alone (N = 196)	Australian patients admitted to 3 Adelaide hospitals with smoking-related illnesses Varenicline + Quitline counselling Quitline counselling	Effectiveness determined through self-reported CA, defined as smoking <5 cigarettes in total during follow-up periods 7PP was collected at end of each week during first month's supply of varenicline (end of first script) Abstinence biologically validated in random sub-set of subjects through exhaled CO levels of <10 ppm Safety and tolerability	Varenicline was well tolerated in inpatient setting among subjects admitted with acute smoking-related illnesses. The most common self-reported AE during 12-week treatment phase was nausea (16.3% in the VT+C group compared with 1.5% in the counselling alone group). Other adverse events include headache (6.1% vs. 1.5%), abnormal dreams (6.1% vs. 1.0%), insomnia (5.1% vs. 2.0%), and vomiting (4.1% vs. 0.5%) in the VT plus counseling and counseling alone groups, respectively. Thirteen deaths occurred during the study period (n = 6 were in the VT+C arm compared with n = 7 in the counselling alone arm). All of these subjects had known comorbidities or developed underlying comorbidities. Proportion of subjects who remained continuously abstinent were significantly greater in VT-C arm (31.1%, n=61) compared with counselling alone (21.4%, n=42; RR 1.45, 95% CI 1.03 to 2.03, p = 0.03).
Chang *et al*, 2017	Prospective cohort study	Varenicline (N = 6,336)) NRT (N = 7,061)	Taiwanese smokers aged 25–54 years and ≥ 55 years participating in Smoking Cessation Program	Self-reported smoking behaviours by telephone interview	Among smokers aged 25–54 years, varenicline users had a greater 7PP abstinence than NRT users (34.0% vs. 23.5%), with adjusted OR ranging from 1.23 (CI: 1.09–1.39; 6-month point-prevalence) to 1.37 (CI: 1.24–1.50; 1-month point-prevalence). Among smokers aged 55 years or older, 7PP was similar for varenicline and NRT users (32.3% vs. 33.1%), and ORs did not suggest that varenicline has greater effectiveness than NRT.
Chang *et al*, 2019	Hospital-based retrospective cohort study	Varenicline (N = 101) NRT (N = 28)	Taiwanese individuals ≥60 years old, with national health insurance and who smoked ≥10 cigarettes per day and visited Mackay Memory Hospital	Smoking status	Three- or six-month point abstinence rate was 48.1%. The proportion of quitters using varenicline was significantly higher than that of non-quitters.

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					Multivariate regression analyses showed that the patients who received varenicline were 3.22 times more likely to quit smoking than those who received NRT
Chengappa *et al*, 2014	Rand, DB, PC [12 wks treatment and 12 wks follow up]	Varenicline 0.5 mg/day for 3 days, 0.5 mg BD for 4 days, then 1 mg BD (N = 31) Placebo (N = 29)	Aged 18-65 years Clinically stable adult patients with DSM-IV bipolar disorder	Primary outcome was 7PP of self-reported no smoking verified by expired CO level <10 ppm Psychopathology and side effects	At end of treatment, significantly more subjects quit smoking with varenicline (48.4%) than with placebo (10.3%) (OR=8.1%; 95% CI, 2.03-32.5%; p<0.002). At end of follow up, 19.4% of varenicline-treated subjects remained abstinent compared to 5.9% assigned to placebo (OR=3.2; 95% CI, 0.60-17.6; p=0.17). Psychopathology scores remained stable. Ten serious AEs occurred (n=6, varenicline; n=4, placebo) Abnormal dreams occurred significantly more often in varenicline-treated subjects (61.3%) than in those receiving placebo (31.6%; Fisher Exact test, p=0.04). Eight varenicline-treated and 5 placebo-treated subjects expressed fleeting suicidal ideation, a nonsignificant difference.
Cinciripini *et al*, 2013	PC, rand [12 wks treatment and 12 wks follow up]	Varenicline 0.5 mg/day for days 1-3, followed by 0.5 mg BD for days 4-7, and 1 mg BD thereafter (N = 86) Bupropion hydrochloride SR, 150 mg/d for days 1-3, followed by 150 mg BD thereafter (N = 102) Placebo (N = 106)	Community volunteers who wanted to quit smoking	Prolonged abstinence from smoking and weekly measures of depression, negative affect, and other symptoms of nicotine withdrawal.	Significant differences were found in abstinence at end of treatment and through 3-month post-quit follow-up visit, favouring both active medications compared with placebo. At 6-month post-quit follow-up visit, only varenicline vs placebo comparison remained significant. Varenicline use associated with generalised suppression of depression and reduced smoking reward compared with other treatments, while both active medications improved concentration, reduced craving, and decreased negative affect and sadness compared with placebo, while having little effect (increase or decrease) on anxiety and anger. No differences were noted in self-reported rates of neuropsychiatric AEs.
Ebbert *et al*, 2015	Rand, DB, PC, multinational clinical trial [24-wk treatment period and 28-wk follow-up]	Varenicline titrated to 1 mg BD (N = 760) Placebo (N=750)	18 years or older, smoked an average of 10 or more cigarettes per day with no continuous abstinence period longer than 3months in the past year, had an exhaled CO level higher than 10 ppm and not willing or able to quit smoking within next month but willing to reduce their smoking and make a quit	Primary efficacy endpoint was CO–confirmed self-reported abstinence during weeks 15 through 24. Secondary outcomes were CO–confirmed self-reported abstinence for weeks 21 through 24 and weeks 21 through 52.	Varenicline group had significantly higher CARs during weeks 15 through 24 vs placebo group (32.1% for varenicline vs 6.9% for placebo; RD, 25.2% [95% CI, 21.4%-29.0%]; RR, 4.6 [95%CI, 3.5-6.1]). Varenicline had significantly higher CARs vs placebo during weeks 21 through 24 (37.8% for varenicline vs 12.5% for placebo ; RD, 25.2% [95% CI, 21.1%-29.4%]; RR, 3.0 [95%CI, 2.4-3.7]) and weeks 21 through 52 (27.0% for varenicline vs 9.9% for placebo; RD, 17.1% [95% CI, 13.3%-20.9%]; RR, 2.7 [95% CI, 2.1-3.5]). Serious AEs occurred in 3.7% of the varenicline group and 2.2% of the placebo group (P = .07).

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
			attempt within next 3 months.		
Nakamura *et al*, 2017 (subgroup of Ebbert *et al*, 2015)	Rand, DB, PC, multinational clinical trial [24-wk treatment period and 28-wk follow-up]	Varenicline titrated to 1 mg BD (N=107) Placebo (N=103)	18 years or older, smoked an average of 10 or more cigarettes per day with no continuous abstinence period longer than 3 months in the past year, had an exhaled CO level higher than 10 ppm and not willing or able to quit smoking within next month but willing to reduce their smoking and make a quit attempt within next 3 months	Primary efficacy endpoint was CO–confirmed self-reported abstinence during weeks 15 through 24. Secondary outcomes were CO–confirmed self-reported abstinence for weeks 21 through 24 and weeks 21 through 52.	CARs for weeks 15 to 24 were higher for participants in the varenicline group versus the placebo group (46.7% vs 12.6%; odds ratio =14.68; 95% CI, 5.38–40.05), and the 7PP of abstinence rates were higher for varenicline versus placebo at week 12 (odds ratio =13.76; 95% CI, 5.28–35.86). The number of participants with a ≥50% reduction in the number of daily cigarettes smoked from baseline to week 4 and a ≥75% reduction by week 8 was greater in the varenicline group versus the placebo group (week 4: 59.8% vs 30.1%; week 8: 38.3% vs 12.6%). Serious adverse events were reported in 3.7% of varenicline participants and 1.0% of placebo participants.
Ebbert *et al*, 2016	Rand, PC trial [12 wks treatment and 12 wks follow up]	Varenicline at dose of 0.5 mg once daily for 3 days, then increased to 0.5 mg BD for days 4‑7 to target dose of 1 mg BD (N = 45) Placebo (N = 48)	Aged ≥18 years or older, smoked 5‑10 cigarettes per day for at least 6 months (light smokers) and were interested in quitting smoking.	Primary endpoint was 7PP smoking abstinence rate at week 12. Expired-air CO level ≤ 8 ppm verified self-reported smoking abstinence. Point prevalence defined as CO-confirmed, self-reported no tobacco use in previous 7 days. Participants who met criteria for 7PP abstinence at weeks 12 and 26 defined as meeting criteria for prolonged abstinence if submitted negative responses to both of following questions: “Since 14 days after your target quit date, have you used any tobacco on each of 7 consecutive days?” and “Since 14 days after your target quit date, have you used any tobacco on at least 1 day in each of 2 consecutive weeks?	At end-of-treatment, 7PP smoking abstinence rate was 53.3% in varenicline group compared to 14.5% in placebo group (OR: 6.69, 95% CI: 2.48–18.06, P <0.001), and prolonged smoking abstinence rate was 40.0% and 8.3%, respectively (OR: 7.33, 95% CI: 2.24–23.98, P = .001). At end-of-study, 7PP smoking abstinence rate was 40.0% in varenicline group compared to 20.8% with placebo (OR: 2.53, 95% CI: 1.01–6.34, P = .047), and prolonged smoking abstinence rate was 31.1% and 8.3%, respectively (OR: 4.97, 95% CI: 1.49–16.53, P = .009). Nausea and sleep disturbance more commonly reported in the varenicline group.
Eisenberg *et al*, 2016	MC, DB, rand, PC trial [12 wks treatment and 12 wks follow up]	Varenicline initiated in hospital at 0.5 mg once/day x 3 days, followed by 0.5 mg BD x 4 days, followed by 1.0 mg BD (N = 151) Placebo (N = 151)	Smoked ≥10 cigarettes/d, motivated to quit smoking and hospitalised with acute coronary syndrome	Primary end point was 7PP smoking abstinence assessed at 24 weeks and biochemical validation using expired CO.	At 24 weeks, patients randomised to varenicline had significantly higher rates of smoking abstinence and reduction than patients randomised to placebo. 7PP abstinence rates were 47.3% in varenicline group and 32.5% in placebo group (P=0.012; NNT=6.8).CARs were 35.8% and 25.8%, respectively (P=0.081; NNT=10.0), and rates of

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
					reduction ≥50% in daily cigarette consumption were 67.4% and 55.6%, respectively (P=0.05; NNT=8.5). AE rates within 30 days of study drug discontinuation were similar between groups (serious AEs: varenicline 11.9%, placebo 11.3%; major adverse cardiovascular events: varenicline 4.0%, placebo 4.6%).
Evins *et al*, 2014	Rand, DB, PC, PG, relapse-prevention clinical trial Participants in open phase who met criteria for biochemically verified, 7PP abstinence at weeks 11 and 12 considered to be CA for at least 14 days were randomised to relapse prevention Intervention [12 wks OL and DB treatment from wks 12 to 52]	Open-label: Varenicline at 0.5 mg per day for 3 days, 0.5 mg BD for 4 days, then 1.0 mg BD Relapse-prevention: Varenicline, 1.0 mg BD (N = 40) Placebo (N =47) Patients received cognitive behaviour therapy	Smokers from community mental health centres with schizophrenia or bipolar disease who had received OL treatment with varenicline	7PP CA at study week 52, end of the relapse-prevention phase, confirmed by exhaled CO. Secondary outcomes were CARs for weeks 12 through 64 based on biochemically verified abstinence and weeks 12 through 76, based on self-reported smoking behaviour.	At week 52, 7PP abstinence rates were 60% in varenicline group (24 of 40) vs 19% (9 of 47) in placebo group (OR, 6.2; 95%CI, 2.2-19.2; P < .001). From weeks 12 through 64, 45% (18 of 40) among those in varenicline group vs 15% (7 of 47) in placebo group were continuously abstinent (OR, 4.6; 95%CI, 1.5-15.7; P = 0.004), and from weeks 12 through 76, 30% (12 of 40) in varenicline group vs 11% (5 of 47) in placebo group were continuously abstinent (OR, 3.4; 95%CI, 1.02-13.6; P = .03). No significant treatment effects on psychiatric symptom ratings or psychiatric AEs.
Evins *et al*, 2019 (subgroup analysis of Anthenelli *et al*, 2016)	Rand, DP, triple-dummy, PC and active-controlled [12 weeks treatment and further 12 weeks non-treatment follow-up]	Nicotine patch; 21 mg per day with taper Varenicline 1 mg BD Bupropion 150 mg BD	Secondary analyses in a subset population, n = 4092, with a primary psychotic (n = 390), anxiety (n = 792), or mood (n = 2910) disorder.	Primary end-point parameters were incidence of prespecified moderate and severe NPSAEs and weeks 9 to 12 CARs	The NPSAE incidence across treatments was 5.1% to 6.3% in those with a psychotic disorder, 4.6% to 8.0% in those with an anxiety disorder, and 4.6% to 6.8% in those with a mood disorder. Neither varenicline nor bupropion was associated with significantly increased NPSAEs relative to NRT or placebo in the psychiatric cohort or any psychiatric diagnostic subcohort. There was a significant effect of treatment on 9–12 CAR (P < 0.0001) and no significant treatment-by-diagnostic subcohort interaction (P = 0.24). Abstinence rates with varenicline were superior to bupropion, NRT, and placebo, and abstinence with bupropion and NRT was superior to placebo. Within-diagnostic subcohort comparisons of treatment efficacy yielded estimated odds ratios for 9–12CAR versus placebo of greater than 3.00 for varenicline, greater than 1.90 for bupropion, and greater than 1.80 for NRT for all diagnostic groups
Gonzales *et al*, 2014	DB, PC, MC [12 wks and 40 wks follow up]	Varenicline (N = 251) Placebo (N = 247)	Healthy adult smokers (≥10 cigarettes/day) with ≥1 prior quit attempt (≥2 weeks) using varenicline	Primary efficacy end point was CO–confirmed (≤10 ppm) CAR for weeks 9–12	CO–confirmed (≤10 ppm) CAR for weeks 9–12 was 45.0% for varenicline vs. 11.8% for placebo (OR: 7.08; 95% CI: 4.34, 11.55; P < 0.0001).

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
		Patients received cognitive behaviour therapy Received individual counselling	and no quit attempts in ≤3 months		Common varenicline group AEs were nausea, abnormal dreams, and headache, with no reported suicidal behaviour.
Heffner *et al*, 2019 (subgroup analysis of Anthenelli *et al*, 2016)	Rand, DP, triple-dummy, PC and active-controlled [12 weeks treatment and further 12 weeks non-treatment follow-up]	Nicotine patch; 21 mg per day with taper Varenicline 1 mg BD Bupropion 150 mg BD	Smokers with BD (I or II) (N = 285) compared to NPC (N = 2,794)	Primary outcomes were occurrence of moderate to severe NPSAEs and Weeks 9–12 biochemically-confirmed CARs	For BD smokers, NPSAE risk differences versus placebo were: varenicline, 6.17 (95% CI: –7.84 to 20.18); bupropion, 4.09 (–8.82 to 16.99); NRT, –0.56 (–12.34 to 11.22). ORs for Weeks 9–12 CA, comparing active medication to placebo among BD smokers were: varenicline, 2.61 (0.68–9.95); bupropion, 1.29 (0.31–5.37), NRT, 0.71 (0.14–3.74). Pooling across treatments, NPSAE occurrence was higher (10.7% versus 2.3%; P < 0.001) and CA rates were lower (22.8% versus 13.3%; P = 0.008) in BD than NPC.
Itani *et al*, 2019	Retrospective analysis of electronic medical records	Varenicline NRT	Patients with and without neurodevelopment disorders aged ≥18 years eligible for smoking cessation prescriptions (N=235,314)	Smoking cessation at two years	Smokers with neurodevelopmental disorders were 48% less likely (95% confidence interval: 42%, 54%) to be prescribed varenicline than NRT, compared to smokers without neurodevelopmental disorders. At 2-year follow-up, smokers with neurodevelopmental disorders prescribed varenicline were 38% more likely to quit smoking (95% confidence interval: 6%, 78%). There was little evidence showing that varenicline increased the likelihood of mental health related adverse events in individuals with neurodevelopmental disorders.
Jiménez-Ruiz *et al*, 2017	Prospective observational study	Varenicline 1 mg twice daily after uptitration (24 weeks)	Spanish patients ≥40 years old with severe of very severe COPD smoking ≥5 cigarettes per day and motivated to quit smoking	CAR, 7PP abstinence	Population completing 24 weeks of treatment: CAR: 36.8%; 7PP abstinence: 65.7%; continuous smoking 31.5% ITT population: CAR: 17.7%; 7PP abstinence 31.6%; continuous smoking: 15.1%; not valid/unknown: 51.8% The most common adverse events included nausea, vivid dreams, stomach ache, insomnia, headache and vomiting.
Jiménez-Ruiz *et al*, 2018	Retrospective cohort study	Varenicline (N = 134) NRT (N = 215) (plus cognitive behavior therapy)	Patients with psychiatric disorders who attended a smoking cessation clinic in Madrid	9-24 weeks CAR	156 subjects achieved 9---24 weeks continuous abstinence (44.7%), in 39% of those who used nicotine patches and in 53.7% of those who used varenicline. OR: 1.64 (95% CI: 1.03---2.61; p = 0.036). Success rates were higher in men; OR 1.85 (95% CI: 1.12---3.04; p = 0.016). High levels of CO and high daily cigarette use were associated with poorer success rates (OR: 0.98, 95% CI: 0.96---0.99, p = 0.007; and OR: 0.98, 95% CI: 0.96---1.00, p = 0.045), respectively. Nausea and pruritus were the most common adverse events. No cases of suicidal ideation or behaviour were found

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
Kotz *et al*, 2017	Retrospective cohort study	Varenicline (N = 3,574) Bupropion (N = 350) NRT (N =10,426)	Smokers with COPD	Cardiovascular and neuropsychiatric adverse events	Neither bupropion nor varenicline showed an increased risk of adverse events compared with NRT. Varenicline was associated with a significantly reduced risk of heart failure (HR=0.56, 95% CI 0.34 to 0.92) and depression (HR=0.73, 95% CI 0.61 to 0.86
Le Mao *et al*, 2019	MC, prospective, DB, rand	Varenicline 1 mg twice daily after uptitration (N = 42) Placebo (N = 39) For 12 weeks (plus intensive counselling)	Current smokers hospitalised for COPD exacerbation	The primary outcome was CAR at week 52. Secondary outcomes included CAR at week 12 and 26, partial abstinence rate (PAR) at week 12, 26 and 52, nicotinic substitute consumption and adverse events	At week 52, CAR was not different in placebo and varenicline groups (25.6%). At week 12, CAR was significantly higher in the varenicline group (50%) as compared to placebo group (27%) (p = 0.041). Nicotine consumption was significantly higher at week 52 in the placebo group (55.3%) as compared to the varenicline group (24.4%) (p = 0.005). There was no significant difference in PAR at week 12, 26 and 52; the frequency of adverse events was similar between the two groups
Mercie *et al*, 2018	Phase 3, MC, Rand, PG, DB, PC	Varenicline (N=123) titrated to two 0.5 mg doses twice daily or placebo (N=125) twice daily for 12 weeks, plus face-to-face counselling. Patients who were not abstinent at week 24 were offered open-label varenicline for 12 additional weeks	PLWH who had smoked ≥10 cigarettes per day for ≥1 year and were motivated to quit smoking,	The primary outcome was the proportion of smokers CA from week 9 to week 48. Smoking status was confirmed by CO in exhaled air. Primary analyses were done in both the ITT population and modified ITT (mITT) population, which comprised all patients who took at least one tablet of their assigned study treatment.	In the ITT analysis, varenicline was associated with a higher proportion of patients achieving CA over the study period (week 9–48): 18 (15%, 95% CI 8–21) of 123 in the varenicline group versus eight (6%, 2–11) of 124 in the placebo group, adjusted odds ratio (OR) 2.5 (95% CI 1.0–6.1; p=0.041). In the mITT analysis, varenicline was also associated with higher CA: 18 (18%, 95% CI 10–25) of 102 versus 8 (7%, 2–12) of 111 in the placebo group (adjusted OR 2.7, 95% CI 1.1–6.5; p=0.029). The incidence of depression was 2.4 per 100 person-years (95% CI 0.6–9.5; two [2%] of 102) in the varenicline group and 12.4 per 100 person-years (95% CI 6.9–22.5; 11 [10%] of 111) in the placebo group. 14 (7%) of 213 participants had 18 cardiovascular events: six (6%) of 102 individuals in the varenicline group and eight (7%) of 111 individuals in the placebo group
Nakamura *et al*, 2007	DB, PC, rand, PG study [12 wks treatment and 40 wks follow up]	Varenicline 0.25 mg BD (N = 153) Varenicline 0.5 mg BD (N = 156) Varenicline 1 mg BD (N = 156) Placebo (N = 154)	Japanese smokers aged between 20 and 75 years who were motivated to stop smoking and who had smoked ≥ 10 cigarettes per day during the preceding year without a period of abstinence >90 days	Primary efficacy variable was CAR, defined as no reported smoking (not even puff) or other nicotine use confirmed by end expiratory CO level ≤10 ppm, during last 4 weeks of treatment (weeks 9–12). Secondary end points included CARs for weeks 9–24 and 9–52. Craving, withdrawal, and smoking satisfaction determined by the	CAR for weeks 9–12 significantly higher for all doses of varenicline compared with placebo (39.5% [51/129]). Highest CAR of 65.4% (85/130) achieved with varenicline 1 mg BD (OR [95% CI] = 2.98 [1.78–4.99]; P < 0.001). CAR for weeks 9–52 significantly greater for varenicline 1 mg BD than placebo (34.6% [45/130] vs 23.3% [30/129]; OR [95% CI] = 1.81 [1.04–3.17]; P = 0.036). CARs for weeks 9–24 at 0.25, 0.5, and 1 mg BD were 33.6% (43/128), 35.2% (45/128), 37.7% (49/130), and for weeks 9–52 at 0.25 and 0.5 mg BD were 27.3% (35/128) and 28.9% (37/128) but failed to reach

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
				Minnesota Nicotine Withdrawal Scale, the Brief Questionnaire on Smoking Urges, and modified Cigarette Evaluation Questionnaire. Tolerability of varenicline also evaluated.	significance versus placebo (29.5% [38/129] for weeks 9–24 and 23.3% [30/129] for weeks 9–52). Treatment-emergent AEs more prevalent among varenicline-treated subjects (79.1% [121/153] at 0.25 mg BD, 80.6% [125/155] at 0.5 mg BD, and 80.1% [125/156] at 1 mg BD) than placebo subjects (71.4% [110/154]). Three most prevalent AEs at varenicline 1 mg BD were nasopharyngitis (35.9% [56/156]), nausea (24.4% [38/156]), and headache (10.3% [16/156]), all of which were mild or moderate intensity. Nausea was only AE that appeared dose related (7.2% [11/153] at 0.25 mg BD, 9.7% [15/155] at 0.5 mg BD, and 24.4% [38/156] at 1 mg BD) versus placebo (7.8% [12/154]).
Politis *et al*, 2018	Prospective, OL, preference-based, PG	Patients chose the smoking cessation intervention they preferred: a standard regimen of varenicline combined with post-discharge advanced behavioural support (group A) or one private consultation session during hospitalisation (group B). Group A: 44 Group B: 57	Adult smokers (>100 cigarettes in their lifetime) and hospitalised due to (a) acute exacerbation of COPD, or (b) bronchial asthma attack, or (c) CAP	Primary outcome was success rate defined as the percentage (%) of smoking abstinence at week 52 and secondary outcomes were (a) changes in quality of life (QoL) indicated by the scores on the Short Form 36 (SF36) questionnaire and (b) predictors of smoking abstinence investigated with multiple binary logistic regression.	Respective abstinence rates were 54.5% and 15.8% at week 12 and 52.3% and 14.0% at week 52. Scores on SF36 were statistically significantly increased in both groups. Predictors of smoking abstinence were varenicline (odds ratio (OR) 7.29; 95% confidence interval (CI) 2.15, 24.77; p = 0.001), age (OR 1.07; 95%CI 1.00, 1.15; p = 0.042), Fagerstrom score (OR 0.37; 95%CI 0.20, 0.68; p = 0.001), SF36 domains "vitality" (OR 1.12; 95%CI 1.04, 1.21; p = 0.003), and "social functioning" (OR 0.95; 95%CI 0.90, 1.00; p = 0.041). Varenicline in combination with behavioural support resulted in high abstinence rates inpatients hospitalised for exacerbation of COPD, asthma attack, or CAP, and improved QoL.
Price *et al*, 2016	OL (12 weeks)	Varenicline 1 mg twice daily after uptitration and five brief behavioural counselling sessions (N = 132)	>18 years of age, had a diagnosis of cancer, reported smoking >5 cigarettes per week, and were interested in quitting smoking.	Self-reports of smoking cessation at week 12 (for the 7 days preceding the assessment) were biochemically confirmed with breath carbon monoxide (CO).	The rate of biochemically verified abstinence at week 12 was 40.2%. Expected side effects were reported (e.g. sleep problems, nausea), but there were no reports of elevated depressed mood, suicidal thoughts, or cardiovascular events. Abstinence was associated with improved cognitive function and reduced negative affect over time (p < 0.05)
Rennard *et al*, 2012	DB, PC, rand study Subjects instructed to quit between Days 8 and 35 after starting medication [12 wks treatment and 12 wks follow up]	Varenicline 0.5 mg once daily for 3 days then 0.5 BD for 4 days then varenicline 1 mg BD (N= 493) Placebo (N = 166)	Smokers of ≥10 cigarettes/day, aged 18–75 years and motivated to quit	Primary endpoint was CO–confirmed CA during Weeks 9–12, and key secondary endpoint was continuous abstinence during Weeks 9–24.	CA was higher for varenicline than for placebo subjects at end of treatment (Weeks 9–12: 53.1% vs. 19.3%; OR 5.9; 95% CI, 3.7–9.4; p < 0.0001) and through 24 weeks follow-up (Weeks 9–24: 34.7% vs. 12.7%; OR 4.4; 95% CI, 2.6–7.5; p < 0.0001). Serious AEs occurred in 1.2% varenicline (none were psychiatric) and 0.6% placebo subjects. Fewer varenicline than placebo subjects reported depression-related adverse events (2.3% vs. 6.7%, respectively).

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
Rigotti *et al*, 2010	MC, rand, DB, PC trial [12 wks treatment and 40 wks follow up]	Varenicline 0.5 mg once daily for 3 days, 0.5 mg BD for 4 days, and then 1.0 mg BD (N = 355) Placebo (N= 359) Subjects received smoking cessation counselling	Adults (35 to 75 years of age) who had smoked an average of ≥10 cigarettes daily in the year before enrollment, wanted to stop smoking but had not tried to quit in the past 3 months, and had stable, documented CVD (other than hypertension) that had been diagnosed for >2 months.	Primary end point was CO–confirmed CAR for weeks 9 through 12 (last 4 weeks of treatment)	CAR was higher for varenicline than placebo during weeks 9 through 12 (47.0% versus 13.9%; OR, 6.11; 95% CI 4.18 to 8.93) and weeks 9 through 52 (19.2% versus 7.2%; OR, 3.14; 95% CI, 1.93 to 5.11). Varenicline and placebo groups did not differ significantly in cardiovascular mortality (0.3% versus 0.6%; difference, -0.3%; 95% CI, -1.3 to 0.7), all-cause mortality (0.6% versus 1.4%; difference,-0.8%; 95% CI, -2.3 to 0.6), cardiovascular events (7.1% versus 5.7%; difference, 1.4%; 95% CI, -2.3 to 5.0), or SAEs (6.5% and 6.0%; difference, 0.5%; 95% CI, -3.1 to 4.1). As a result of AEs, 9.6% of varenicline and 4.3% of placebo participants discontinued study drug.
Schnoll *et al*, 2019	PC, rand	Varenicline for 12 weeks and placebo for 12 weeks (standard [ST]) (N = 102) Varenicline for 24 weeks (extended [ET]) (N = 105) (Counselling sessions)	Cancer patients who smoke	Primary outcomes were 7-day biochemically confirmed abstinence at weeks 24 and 52. Treatment adherence and side effects, adverse and serious adverse events, and blood pressure were assessed	Point prevalence and CA quit rates at weeks 24 and 52 were not significantly different across treatment arms (Ps > 0.05). Adherence (43% of sample) significantly interacted with treatment arm for week 24 point prevalence (odds ratio [OR] = 2.31; 95% confidence interval [CI], 1.15-4.63; P = 0.02) and CA (OR = 5.82; 95% CI, 2.66-12.71; P < 0.001). For both outcomes, adherent participants who received ET reported higher abstinence (60.5% and 44.2%) vs ST (44.7% and 27.7%), but differences in quit rates between arms were not significant for nonadherent participants (ET: 9.7% and 4.8%; ST: 12.7% and 10.9%). There were no significant differences between treatment arms on side effects, adverse and serious adverse events, and rates of high blood pressure (Ps > 0.05).
Steinberg *et al*, 2011	Rand, DB, PC pilot trial [12 wks treatment and 12 wks follow up]	Varenicline 0.5 mg daily for 3 days, then 0.5 mg BD for 4 days, then 1 mg BD (N = 40) Placebo (N = 39) In person behavioural treatment in hospitalised patients	Patients admitted to the hospital who smoked 10 cigarettes or more per day within the past month, were not being discharged into a setting of forced abstinence (e.g. institutionalised), and could attend a 4-week outpatient follow-up visit (e.g. not moving out of the area)	Primary outcome was biochemically confirmed abstinence at 24 weeks following discharge. Secondary outcomes included withdrawal symptoms, motivation, utilisation of treatment, and medical events.	Overall abstinence at 24 weeks was 27% with no difference between varenicline and placebo treatment groups (23% vs. 31%). No significant differences in motivation to stop smoking or withdrawal symptoms. Over 40% of all subjects utilised post-discharge behavioural treatment with significantly higher abstinence rates compared with those who did not (53.1% vs. 8.5%, p<0.01). Overall AEs were similar in both treatment groups with only significant difference being more nausea in varenicline group (25% vs. 5%; p<0.01). Twenty-three subjects re-hospitalised with no significant differences between treatment groups (13 varenicline vs. 10 placebo).
Tashkin *et al*, 2011a	DB multinational trial	Varenicline 0.5 mg daily for 3 days, then 0.5 mg BD for 4 days, then 1 mg BD (N = 250)	Aged ≥ 35 years, smoked an average of ≥10 cigarettes per day in the	Primary end point was CO-confirmed CAR for weeks 9 to 12. Secondary	CAR for weeks 9 to 12 was significantly higher for patients in varenicline group (42.3%) than for those in placebo group (8.8%) (OR, 8.40; 95% CI, 4.99-14.14; P<0.0001).

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
	[12 wks treatment and 40 wks follow up]	Placebo (N = 254)	past year with no period of abstinence > 3 months and had mild to moderate COPD (postbronchodilator FEV_1 /FVC, <70%; FEV_1 percent predicted normal value, ≥50%) and without known psychiatric disturbances	end point was CAR for weeks 9 to 52.	CAR in patients treated with varenicline remained significantly higher than in those treated with placebo through weeks 9 to 52 (18.6% vs 5.6%) (OR, 4.04; 95% CI, 2.13-7.67; P <0.0001). Nausea, abnormal dreams, upper-respiratory tract infection, and insomnia were most commonly reported AEs for patients in varenicline group. Serious AEs were infrequent in both treatment groups. Two patients in varenicline group and one patient in placebo group died during study. Reports of psychiatric AEs were similar for both treatment groups.
Tashkin *et al*, 2011b				Secondary endpoints were mean changes from baseline in post-bronchodilator forced FEV_1 and CCQ scores	Change from baseline in post-bronchodilator FEV_1 was significantly improved in continuous abstainers (121.8 mL) vs. continuous smokers (37.9 mL) at Week 12 (P = 0.0069), but not at Weeks 24 or 52. Mean change from baseline at Week 12 in CCQ Total Score was significantly better in continuous abstainers (-1.04) vs. continuous smokers (-0.53; P < 0.0001): this improvement was sustained at Weeks 24 and 52.
Taylor *et al*, 2017	Prospective cohort study of electronic medical records from 654 general practices in England	Varenicline NRT	Aged ≥18 years and prescribed varenicline or NRT	Primary outcome was smoking cessation at 2 years' follow-up; outcome was also assessed at 3, 6, and 9 months, and at 1 and 4 years after exposure.	At 2 years, 28.8% (N = 20,362/70,610) of participants prescribed varenicline and 24.3% (N =36,268/149,526) of those prescribed NRT quit; adjusted odds ratio was 1.26 [95% confidence interval (CI): 1.23 to 1.29], P < 0.0001. The association persisted for up to 4 years and was consistent across all analyses.
Taylor *et al*, 2020	Prospective cohort study of electronic medical records from 654 general practices in England	Varenicline NRT	Aged ≥18 yearsS Smokers and nonsmokers included for smoking prevalence estimate., Smokers prescribed either varenicline or NRT included for effectiveness/safety estimates. Patients categorised as having mental disorder if: (1) they had been diagnosed with one of following common mental disorders 365 days before first varenicline/NRT prescription: depression, neurotic disorder, (2) if they had a lifetime record	Outcomes were smoking cessation, and incidence of neurotic disorder, depression, prescription of antidepressants, or hypnotics/anxiolytics. Follow-ups were 3, 6, and 9 months, and at 1, 2, and 4 years.	Seventy-eight thousand four hundred fifty-seven smokers with mental disorders aged ≥18 years were prescribed NRT (N = 59,340) or varenicline (N = 19,117) from September 1, 2006 to December 31, 2015. Compared with smokers without mental disorders, smokers with mental disorders had 31% (95% CI: 29% to 33%) lower odds of being prescribed varenicline relative to NRT but had 19% (95% CI: 15% to 24%) greater odds of quitting at 2 years when prescribed varenicline relative to NRT.

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
			of bipolar disorder, or schizophrenia or other nonaffective psychotic disorders, or (3) if they were prescribed any of following medications 365 days before smoking cessation medication prescription: antidepressants, antipsychotics, hypnotics or anxiolytics, or mood stabilisers. Patients with no record of above listed mental disorders or psychoactive medication prescriptions considered to have no mental disorder		
Tonstad *et al*, 2006	Rand, controlled trial [12 wks treatment and 40 wks follow up]	Varenicline 1 mg BD (N = 603) Placebo (N = 607)	Cigarette smokers between ages of 18 and 75 years treated for 12 weeks with OL varenicline titrated to 1 mg BD who did not smoke, use tobacco, or use NRT during last week of treatment Varenicline: 603 Placebo: 607	CO–confirmed CA during weeks 13 to 24 and weeks 13 to 52 of study.	CO-confirmed CAR was significantly higher for varenicline group than for placebo group for weeks 13 to 24 (70.5% vs 49.6%; OR, 2.48; 95% CI, 1.95-3.16; P<0.001) as well as for weeks 13 to 52 (43.6% vs 36.9%; OR, 1.34; 95% CI, 1.06-1.69; P=0.02). Adverse events reported in OL period were mostly mild; no difference in adverse events between varenicline and placebo was observed during DB period.
Tuisku *et al*, 2016	Rand, PC (varying treatment periods dependent on treatment and 14 wk follow-up)	Light dependence: Nicotine patch 10 mg/16 hours for 8 wks (N = 93) Placebo (N = 86) Stronger dependence: Varenicline for 12 wks: 0.5 mg once daily for 3 days and then 0.5 mg BD till the end of the first week then 1 mg BD (N = 60) Nicotine patch 15 mg/16 hours for 8 wks (N = 49)	Aged 18- to 26-year-old, had smoked daily for at least the past month and smoked 100 or more cigarettes in their life and were motivated to quit smoking	Primary outcome was self-reported smoking abstinence at week 12. Secondary outcomes were self-reported smoking abstinence at weeks 4 and 26, and self-reported abstinence verified by saliva cotinine level at week 12.	Prevalence of self-reported smoking abstinence did not differ statistically significantly in light smokers during follow-up (week 4: 19.8% for placebo patch and 26.6% for nicotine patch 10 mg/16 hr; week 12: 17.4% versus 23.4%; week 26: 15.1% versus 20.2%), but groups of heavy smokers differed significantly for 12 weeks (week 4: 19.6% for nicotine patch 15 mg/16 hr and 73.3% for varenicline, p < 0.001; week 12: 15.7% versus 36.7%, p = 0.018). This statistically significant difference did not endure for entire follow-up (week 26: 9.8% versus 18.3%, p = 0.280). However, saliva cotinine verified abstinence at week 12 did not support self-reported abstinence.
Tulloch *et al*, 2016	Parallel, three-group rand controlled, SC	Varenicline: 0.5 mg once daily for 3 days, increasing to 0.5 mg BD for days 4–7, followed by a	18 years or older, smoked ≥10 cigarettes per	Primary outcome was CO-confirmed CAR from weeks 5–52.	CARs for weeks 5–52 were 10.0%, 12.4%, and 15.3% in NRT, NRT+, and varenicline groups, respectively; no group differences were observed. Results with 7PP showed that

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
	(Ottawa Heart Institute) study [varying treatment periods dependent on treatment and 40 wk follow-up]	maintenance dose of 1 BD for 11 wks (N =247 NRT group (10 wks): If smoked ≥ 20 cigarettes/day- 21 mg/day for 6 weeks, 14 mg/day for 2 weeks, and 7 mg/day for 2 weeks. If smoked < 20 cigarettes/day - 14 mg/day for 6 wks and 7 mg/day for 4 wks. (N = 245) NRT+ group: similar to NRT group; however withdrawal symptoms to be controlled by titrating NRT to daily maximum of 35 mg via patches and to use gum or inhalers freely. Minnesota Nicotine Withdrawal Scale used to assist participants and staff to titrate dosing at each visit; scores ≥ 2 on any item signaled need to increase dosage. If interested and recommended by study nurse or physician, participants could continue to receive treatment for up to 22 wks. (N = 245)	day, and were willing to make a quit attempt in the next 2–4 weeks.	Secondary outcomes were: CAR from weeks 5–10 and 5–22, and CO-confirmed 7PP at weeks 10, 22, and 52.	varenicline was superior to NRT at week 52 (OR, 1.84; 97.5% CI, 1.04–3.26) in adjusted ITT analysis. Those in varenicline group had higher CAR at weeks 5–22 (OR, 2.01; CI, 1.20–3.36) than those in NRT group. Results with 7PP revealed that both NRT+ (OR, 1.72; CI, 1.04–2.85) and varenicline (OR, 1.96; CI, 1.20–3.23) were more effective than NRT at 22 weeks. As compared to NRT monotherapy, NRT+ and varenicline produced significant increases in CAR for weeks 5–10 (OR, 1.52; CI, 1.00–2.30 and OR, 1.58; CI, 1.04–2.39, respectively); results were similar, but somewhat stronger, when 7PP used at 10 weeks (OR, 1.57; CI, 1.03–2.41 and OR, 1.79; CI, 1.17–2.73, respectively). All medications were well tolerated, but participants in the varenicline group experienced more fatigue, digestive symptoms (e.g., nausea, diarrhoea), and sleep-related concerns (e.g., abnormal dreams, insomnia), but less dermatologic symptoms than those in the NRT or NRT+ groups. The frequency of SAEs did not differ between groups.
Wang *et al*, 2009	Rand, DB, PC [12 wks treatment and 12 wks follow up]	Varenicline 0.5 mg daily for first 3 days; 0.5 mg BD for next 4 days; and 1 mg BD from day 8 (N = 165) Placebo (N = 168)	Smokers from China, Singapore and Thailand Varenicline: 165 Placebo: 168	Primary study end-point was 4-week CAR defined as proportion of subjects who reported total abstinence from smoking and other nicotine products from weeks 9–12. Key secondary end-point was CAR from weeks 9–24, defined as proportion of subjects who achieved primary end-point as well as total abstinence from all tobacco products from weeks 13–24.	Both end-points achieved by significantly higher proportion of subjects in varenicline group than in placebo group. The 4-week CAR endpoint achieved by 50.3% and 31.6% in varenicline and placebo groups, respectively (P = 0.0003), while CAR from weeks 9–24 achieved by 38.2% and 25.0% of subjects, respectively (P = 0.0080). Varenicline was safe and appeared to be well tolerated by most subjects.
Westergard *et al*, 2015	Rand, DB, PC [12 wks treatment and 12 wks follow up]	Varenicline 0.5 mg once daily for 3 days then 0.5 mg BD till the end of the first week then 1 mg BD (N = 26) Placebo (N = 26)	Asthmatic, current smokers, age 19-40, ≥10 cigarettes daily ≥10 packyears	Evaluation of smoking status, asthma symptom score, general health quality score and methacholine challenge were performed at week 0, week 6, week 12 and week 24.	In varenicline group, at week 12, 69% of the patients quit smoking vs. 36% in placebo group (p = 0.017, ITT analysis), but after 24 weeks, a high relapse rate was present (quit rates 19% vs. 16%, NS). After 6 weeks of treatment, significant improvements in airway hyper-responsiveness in varenicline group was found (from 88% to 58%, p = 0.016), whereas no change was observed in placebo group. Symptom score and general health quality improved in both varenicline and placebo group.

Trial identifier	Design [Duration]	Treatment regimens	Patient population	Key efficacy outcome measures	Results
Williams *et al*, 2012	Rand, DB [12 wks treatment and 12 wks follow up]	Varenicline 0.5 mg once daily for 3 days then 0.5 mg BD for 4 days then 1 mg BD (N = 85) Placebo (N = 43)	Patients aged 18-75 years, with schizophrenia or schizoaffective disorder, smoked ≥15 cigarettes per day and had no period of smoking cessation > 3 months over previous year	Primary outcome was safety and tolerability of varenicline assessed as AE frequency and changes in ratings on Positive and Negative Syndrome Scale and other psychiatric scales from baseline to 24 weeks Abstinence defined as no smoking 7 days prior to week 12 and 24, verified by CO level.	At 12 weeks, 19% of varenicline-treated patients met smoking cessation criteria versus 4.7% of placebo-treated patients (p=0.046). At 24 weeks, 11.9% varenicline-treated and 2.3% placebo-treated patients met abstinence criteria (P=0.09). Total AE rates were similar between groups, with no significant changes in symptoms of schizophrenia or in mood or anxiety ratings. Rates of suicidal ideation AEs were 6% (varenicline) and 7% (placebo) (P=1.0). There was 1 suicide attempt by a varenicline patient with a lifetime history of similar attempts and no completed suicides.
Wong *et al*, 2012	MC, DB, PC [12 wks treatment and 12 months follow up]	Varenicline: days 1–3: 0.5 mg once daily; days 4–7: 0.5 BD; and days 8–12 weeks: 1 mg BD (N = 151) Placebo (N = 135)	Aged ≥18 years who attended preoperative clinics of the Toronto Western Hospital and Mt. Sinai Hospital, Toronto, Ontario, Canada, who were scheduled for elective ambulatory or inpatient general surgical, orthopaedic, urologic, plastic, gynaecologic, ophthalmologic, or neurosurgical procedures. Scheduled for surgery within 8–30 days, smoked ≥10 cigarettes per day during previous year, and had no period of smoking abstinence > 3 months in past year.	Primary outcome was 7PP abstinence rate 12 months after surgery. Secondary outcomes included abstinence at 3 and 6 months after surgery.	7PP abstinence at 12 months for varenicline versus placebo was 36.4% versus 25.2% (relative risk: 1.45; 95%: CI: 1.01–2.07; P = 0.04). At 3 and 6 months, 7PP abstinence was 43.7% versus 31.9% (relative risk: 1.37; 95% CI: 1.01 to 1.86; P=0.04), and 35.8% versus 25.9% (relative risk: 1.43; 95%: CI 1.01–2.04; P=0.04) for varenicline versus placebo, respectively. Treatment with varenicline (OR: 1.76; 95% CI: 1.03–3.01; P = 0.04), and preoperative nicotine dependence (OR: 0.82, 95% CI: 0.68 to 0.98; P=0.03) predicted abstinence at 12 months. AE profile in both groups was similar except for nausea, which occurred more frequently for varenicline versus placebo (13.3% vs. 3.7%, P=0.004).
Zawertailo *et al*, 2020	Rand, DB [12 weeks]	Varenicline (N=16) Placebo (N=15)	Aged 18 to 65 years, current daily smokers ≥10 cigarettes per day; in treatment for alcohol dependence	The primary outcome was abstinence from smoking at end of treatment, defined as no smoking at during last 4 weeks of treatment. Smoking abstinence was assessed each week using the 7PP abstinence	Only one subject in the placebo group quit by end of treatment (7PP abstinence), compared with 7 in the varenicline group (χ^2 (1) = 5.56, P = 0.037). Both groups had a significant decline in cigarettes per day (CPD) by end of treatment (varenicline = 22.1 ± 13.3 to 2.0 ± 3.0 CPD, *t*(10) = 4.45, P = 0.001; placebo: 14.9 ± 4.4 to 5.3 ± 6.3 CPD, *t*(13) = 3.61, P = 0.003).

Abbreviations: 7PP, 7 point prevalence; AD, anxiety disorder; AE, adverse event; ART, antiretroviral therapy; BD, bipolar disorder; BID, twice daily; CAP, community-acquired pneumonia; CA, continuously abstinent /continuous abstinence; CAR, Continuous Abstinence Rate; CCQ, clinical COPD questionnaire; CI, confidence interval; C-NRT, combined nicotine patches and lozenges; CO, carbon monoxide; COPD, chronic obstructive airways disease; DB double-blind; FEV1, forced expiratory volume in one second; FEV_1/FVC, Tiffeneau-Pinelli index- proportion of vital capacity able to expire in first second of forced expiration; FVC, forced vital capacity; GAD, generalised anxiety disorder; ITT, intention-to-treat; MC, multicentre; NNT, number needed to treat; NPC, nonpsychiatric disorders; NRT, nicotine replacement therapy; NRT+, patches and inhaler or gum; NPSAEs,

neuropsychiatric adverse events; OL, open-label; OR, odds ratio; PC, placebo-controlled; OTS, Ontario Tobacco Survey; PD, panic disorder; PG, parallel group; PLWH, people living with HIV/AIDs; ppm, parts per million; PTSD, posttraumatic stress disorder; Rand, randomised; RD, risk difference; RR, relative risk; SAE, serious adverse event; SC, single centre; SR, sustained release; TQD, target quit date; VT-C, varenicline tartrate plus counselling; wk, week; wks, weeks

3.3 Clinical evidence of varenicline in combination with nicotine replacement therapy

Three randomised controlled trials combination varenicline in combination with nicotine replacement therapy with varenicline replacement therapy:

> Hajek P, Mith KM, Dhanjo AR and McRobbie H. Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial. BMC Medicine, 2013, 11:140
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> Koegelenberg CFN, Noor F, Batemen ED, van Zyl-Smit RN, Bruning A. O'Brien JA, Smith C, Abdool-Gaffar MS, Emanuel S, Esterhuizen TM and Irusen EM. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation. A randomized clinical trial. JAMA, 2014;312(2):155-161.
>
> Ramon JM, Morchon S, Baena A and Masuet-Aumatell C. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. BMC Medicine 2014, 12:172

Two further publications presented observational and cohort analyses (respectively) of varenicline in combination with nicotine replacement therapy:

> Berg KM, Jorenby DE, Baker TB and Fiore MC. Triple smoking cessation therapy with varenicline, nicotine patch and nicotine lozenge: a pilot study to assess tolerability, satisfaction and end-of-treatment quit rates. Journal of Smoking Cessation, 2017; 13(3):145–153.
>
> Ebbert JO, Burke MV, Hays JT and Hurt RD. Combination treatment with varenicline and nicotine replacement therapy. Nicotine & Tobacco Research, 2009; 11(5):572–576.

Presented in **Table 16** is a summary of the trials which studied varenicline in combination with nicotine replacement therapy. These studies are also summarised in **Figure 11** and **Figure 12**.

Table 16: Characteristics of studies of varenicline in combination with NRT

Trial identifier	Design (duration)	Treatment regimens	Patient population	Key outcome measures
Randomised controlled trials				
Hajek *et al*, 2013	Double-blind, randomised controlled trial (12 weeks)	Varenicline 0.5 mg/d for the first 3 days, 1 mg/d on days 4–7, followed by 2 mg/d for the rest of the 12-weeks course + nicotine (15 mg/16 hours) [N=58] Varenicline (as above) + placebo patch [N=59] Subjects started varenicline 1 week before their TQD and were randomised to NRT or placebo on the TQD Subjects received weekly support sessions.	Smokers ≥18 years old seeking treatment for smoking cessation	Abstinence at 24 hours and 1 week post-TQD defined as no smoking at all, validated by expired carbon monoxide (CO) reading of <9ppm. Abstinence at 4 weeks defined in accordance with the Russell Standard, i.e. sustained abstinence since TQD validated by CO reading at all points where CO readings were scheduled (i.e. weeks 1–4 post-TQD), or if a session was missed, self-reported sustained abstinence and validation by a CO reading at the next attendance. Up to 5 lapses (single instances of smoking) since the TQD were allowed with no smoking at all during Week 4. Participants who did not provide a CO reading at week 4 were considered to be smoking. Participants lost to follow-up were considered to be smoking. Abstinence at 12 weeks was defined as self-reported sustained abstinence since TQD (with up to 5 lapses allowed) but it was not biochemically validated.
Koegelenberg *et al*, 2014	Double-blind, randomised placebo-controlled trial (12 weeks treatment and 12 weeks non-treatment follow-up)	Varenicline 0.5 mg once daily for 3 days, titrated to 0.5 mg twice daily for days 4 to 7 and then to maintenance dose of 1 mg twice daily through week 12. Varenicline was tapered off and stopped at the end of week 13 (0.5 mg twice daily for 4 days, followed by 0.5 mg in the evenings for 3 days; total duration, 14 weeks). Varenicline was initiated one week before TQD Nicotine patches 15-mg or placebo patches were administered for 16 h/d (beginning two weeks before TQD)	Participants aged 18 to 75 years who sought assistance with smoking cessation, had smoked at least 10 cigarettes/day during previous year and month prior to screening, and had had no period of smoking abstinence longer than 3 months in past year were eligible	Primary end point was 4-week exhaled carbon monoxide–confirmed continuous abstinence rate for weeks 9 through 12 of treatment, i.e., the proportion of participants able to maintain complete abstinence from smoking for last 4 weeks of treatment. Secondary end points included point prevalence abstinence at 6 months, continuous abstinence rate from weeks 9 through 24, and adverse events.

Trial identifier	Design (duration)	Treatment regimens	Patient population	Key outcome measures
Ramon *et al*, 2014	Randomised, placebo-controlled clinical trial (12 weeks)	Varenicline beginning one week before the TQD: 0.5 mg once daily for three days, then 0.5 mg twice daily for four days, followed by 1 mg twice daily for eleven weeks (N = 170) The smokers received identical packages of either nicotine 21 mg/24 hours or placebo patches for 11 weeks (N = 171)	Smoker ≥ 18 years old who were seeking treatment in an outpatient smoking cessation clinic having smoked ≥20 cigarettes daily for the last six months and had no period of smoking abstinence longer than three months in the last year.	Primary end point was continuous abstinence defined as not smoking throughout the follow-up period from week 2 (1 week after the quit date) to week 12. The criteria for determining continuous abstinence were not having smoked since week 2 and showing CO concentrations of <10 ppm at 12 weeks. Subjects who failed to provide validation data were considered relapsed. The secondary end points were point prevalence, defined as abstinence during the week before the follow-up visits at 8, 12 and 24 weeks, the continuous abstinence rate from week 2 through 24, and the incidence of adverse events.
Observational studies				
Berg *et al*, 2017	Observational study (12 weeks)	1. Varenicline 0.5 mg once daily for 3 days; followed by 0.5 mg twice daily for 4 days; followed by 1 mg twice daily for 11 weeks. 2. Transdermal nicotine 21 mg for 8 weeks (starting on the TQD); followed by transdermal nicotine 14 mg for weeks; followed by transdermal nicotine 7 mg for 2 weeks (Note: for participants smoking 5–9 cigarettes/day at baseline, the regimen was 14 mg/day for 10 weeks followed by 7 mg/day for 2 weeks). 3. Nicotine mini lozenges (2 mg) used as needed for relief of withdrawal and craving, for 12 weeks (starting on the TQD). Participants were urged to use at least four mini lozenges per day, but no more than 20 per day. N=36	Aged > 17 years Smoked ≥five cigarettes/day for the previous 6months Alveolar CO ≥ 6 ppm	Point prevalence abstinence was defined as participant-reported not smoking in the 7 days prior to the week 12 follow-up call. Prolonged abstinence was defined as participant-reported continuous abstinence from Week 2 through Week 12, provided the participant was contacted on Week 12. If they smoked at all between Week 2 through Week 12, or had incomplete data, they were assumed smoking for the prolonged abstinence variable.
Ebbert *et al*, 2009	Observational study	Varenicline NRT N = 104	Reviewed clinical experience of two groups of cigarette smokers enrolled in residential tobacco treatment program: (a) patients receiving combination treatment with varenicline and NRT (*N* =	Smoking abstinence rates – self-report

Trial identifier	Design (duration)	Treatment regimens	Patient population	Key outcome measures
			104) and (b) usual-care patients receiving treatment before the release of varenicline (*N* = 135).	

Abbreviations; ppm, parts per million; NRT, nicotine replacement therapy; TQD, target quit date

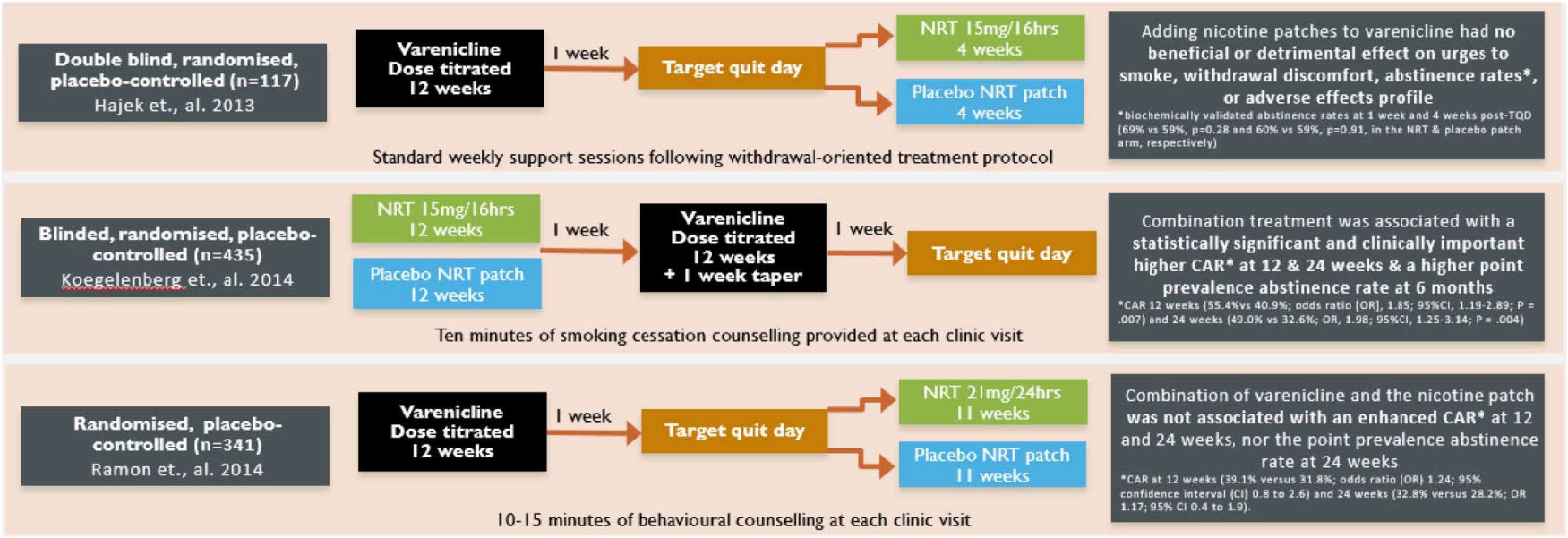

Figure 11: Randomised controlled trials with varenicline + NRT combination therapy

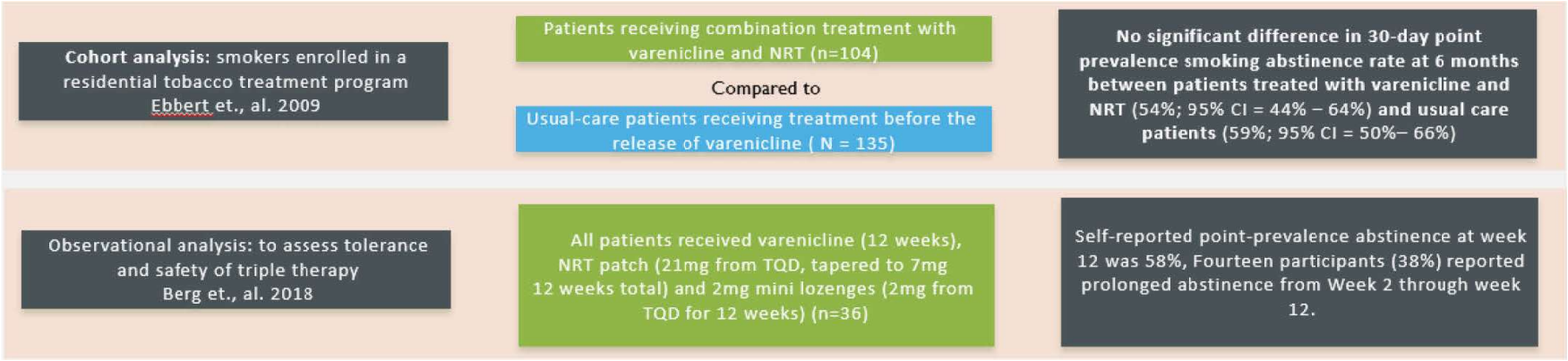

Figure 12: Observational studies with varenicline + NRT combination therapy

Efficacy

Randomised controlled trials

Hajek et al (2013)

Effect of varenicline and NRT combination on abstinence rates

Table 17 shows the rates of continuous validated abstinence (not a puff since the TQD) at 24 hours and 1 week and the Russell Standard sustained validated abstinence at 4 weeks (up to 5 cigarettes allowed with no smoking during the previous week). There were no differences between the two study arms at any time point. Self-reported sustained abstinence rates at 12 weeks were 29% vs. 36% in the placebo and NRT patch groups, respectively (x^2 = 0.73; p = 0.39).

Table 17: Effect of varenicline + NRT combination on abstinence rates

Period after TQD	Placebo patch N=59	Nicotine patch N=58	Pearson Chi-square; p-value
24 hours N (%)	47 (80)	46 (79)	x^2 = .00; p = 0.96
1 week N (%)	35 (59)	40 (69)	x^2 = 1.18; p = 0.28
4 weeks N (%)	35 (59)	35 (60)	x^2 = 0.01; p = 0.91

TQD, target quit date
Source: Hajek et al, 2013, Table 3

Adverse events

There were no differences in ratings of nausea between the two groups at any time point (1.6 vs 1.5, 1.7 vs 1.8 and 1.5 vs 1.4 at 24 hours, 1 week and 4 weeks after TQD in the placebo patch and NRT patch arm, respectively, all NS). There was one serious adverse event in the placebo arm (musculoskeletal injury) that was unrelated to the study medication. **Table 18** shows other adverse events reported by more than 5% of participants.

Table 18: Effect of varenicline + NRT combination on adverse events

AE reported	Number of participants experiencing the problem		Pearson Chi-square; p-value
	Placebo patch N=59	Nicotine patch N=58	
Abnormal dreams	5	12	x^2 = 3.5; p = 0.06
Headache	4	6	x^2 = .48; p = 0.49
Insomnia	11	11	x^2 = .00; p = 0.97
Nausea	26	33	x^2 = 1.93; p = 0.17

Source: Hajek et al, 2013, Table 4

Koegelenberg et al (2014)

Abstinence Rates and Craving for Cigarette Smoking

The continuous and the point prevalence abstinence rates for the per-protocol and multiple imputation analyses are presented in **Table 19**. Participants who received active NRT and varenicline were more likely to achieve continuous abstinence at 12 weeks (55.4% vs 40.9%; P = .007) and 24 weeks (49.0% vs 32.6%; P = .004) and point prevalence abstinence at 24 weeks (65.1% vs 46.7%; P = .002) than those receiving placebo NRT and varenicline. The differences

observed in continuous abstinence were 14.5% (95% CI, 5.2%-23.8%) at 12 weeks and 16.4% (95% CI, 7.2%-25.5%) at 24 weeks, and the numbers needed to treat (NNT) to achieve 1 additional successful attempt at smoking cessation were 7 (95% CI, 5-20) and 7 (95% CI, 4-14), respectively. The difference observed in point prevalence abstinence at 24 weeks was 18.4% (95% CI, 9.5%- 27.9%) and the NNT, 6 (95% CI, 4-11). Results of the intention-to-treat analysis of the primary end point provided similar results. Continuous abstinence at 12 weeks was observed in 99 of 222 participants (44.6%; 95% CI, 38.0%%-51.4%) vs 70 of 224 participants (31.3%; 95% CI, 25.3%-37.8%) randomised to receive the addition of NRT vs placebo, respectively (OR, 1.77; 95% CI, 1.18-2.66; P = .004).

Table 19: Continuous abstinence and point prevalence abstinence rate (N = 435)

		Per-protocol analysis				Multiple imputation analysis of main outcomes			
		No. (%)				No. (%)[a]			
Time since TQD	Time period	Varenicline and active nicotine patch (N=216)	Varenicline and placebo patch (N=219)	OR (95% CI)	P value	Varenicline and active nicotine patch (N=216)	Varenicline and placebo patch[b]	OR (95% CI)	P value
Continuous abstinence									
8 weeks	Weeks 5-8	96 (44.4)	76 (34.7)	1.50 (1.02-2.22)	.04				
12 weeks	Weeks 9-12	99 (45.8)	70 (32.0)	1.80 (1.22-2.66)	.003	120 (55.4)	90 (40.9)	1.85 (1.19-2.89)	.007
16 weeks	Weeks 9-16	84 (38.9)	56 (25.6)	1.85 (1.23-2.79)	.003				
24 weeks	Weeks 9-24	71 (32.9)	42 (19.2)	2.06 (1.33-3.21)	.001	106 (49.0)	71 (32.6)	1.98 (1.25-3.14)	.004
Point prevalence abstinence rates									
1 week	Week 1	69 (31.9)	61 (27.9)	1.22 (0.81-1.83)	.35				
2 weeks	Week 2	98 (45.4)	95 (43.4)	1.08 (0.74-1.58)	.68				
4 weeks	Week 4	110 (50.9)	87 (39.7)	1.57 (1.08-2.30)	.02				
8 weeks	Week 8	109 (50.5)	96 (43.8)	1.31 (0.90-1.90)	.17				
12 weeks	Week 12	116 (53.7)	87 (39.7)	1.76 (1.20-2.58)	.003	138 (63.9)	112 (51.2)	1.68 (1.07-2.66)	.03
16 weeks	Week 16	104 (48.1)	81 (37.0)	1.58 (1.08-2.32)	.02				
24 weeks	Week 24	94 (43.5)	63 (28.8)	1.91 (1.28-2.84)	.001	141 (65.1)	101 (46.7)	2.13 (1.32-3.43)	.002

Abbreviations: OR, odds ratio; TQD, target quit date.

a. *Calculated mean proportional values (numbers rounded) derived from data of participants who completed follow-up to 12 and 24 weeks, respectively, and, to account for missing data, 5 sets of imputed values for the participants who did not attend their 12- and 24-week follow-up visits. Data for 2 participants (in the placebo group) were insufficient to perform the multiple imputation analysis at 24 weeks.*

b. *n = 219 at 12 wk and n = 217 at 24 wk.*

Source: Koegelenberg et al, 2014, Table 2

Safety and tolerability

The mean weight gain in those who completed 6 months of follow-up was 3.0 kg (95% CI, 2.3-3.8 kg) in the active and 2.2 kg (95% CI, 1.7-2.8 kg) in the placebo NRT groups, respectively (*P* = .09). Other adverse events that were observed at any time during the treatment phase or follow-up are summarised in **Table 20**. Skin reactions reported in the active NRT patch group included localised erythema (n = 21) or itch (n = 6), whereas 3 patients experienced mild generalised reactions and a single participant reported worsening of pre-existing acne. Cutaneous adverse events in the placebo NRT patch group included localised erythema (n = 11) or itch (n = 2), mild generalised dermatitis (n = 3), and gingivitis (n = 1).

Table 20: Adverse events reported in at least 2% of participants per study group

	No. (%)		
Adverse event	**Varenicline and active nicotine patch N=216**	**Varenicline and placebo patch N=219**	**P value**
Nausea	59 (27.3)	54 (24.7)	.53
Insomnia and disturbed sleep	43 (19.9)	35 (15.1)	.18
Abnormal dreams	10 (4.6)	13 (5.9)	.54
Headaches	17 (7.9)	22 (10.0)	.43
Any skin reactions	31 (14.4)	17 (7.8)	.03
Constipation	9 (4.1)	6 (2.7)	*.42*
Depression	5 (2.3)	3 (1.4)	.50[a]

Source: Koegelenberg et al, 2014, Table 3

Ramon et al (2014)

Primary and secondary endpoints

Table 21 shows both the continuous and point abstinence rates. A comparison of the intervention and control groups for the continuous abstinence rates at 8, 12 and 24 weeks (Table 2) revealed no statistically significant differences (OR 1.04, 95% CI 0.4 to 2.1; OR 1.24, 95% CI 0.8 to 2.6; and OR 1.17 95% CI 0.4 to 1.9, respectively). Additionally, when the groups were compared for point abstinence, the results were similar and not statistically significant (**Table 20**).

Table 21: Smoking abstinence by group

	Continuous abstinence[a]			Seven-day point-prevalence abstinence		
Group	**Abstainers (%)**	**Crude OR (95% CI)**	**OR[b] (95% CI)**	**Abstainers (%)**	**Crude OR (95% CI)**	**OR[b] (95% CI)**
Week 8						
Varenicline + nicotine patch (N =170)	72 (42.2%)	1.08 (0.7 to 1.7)	1.04 (0.4 to 2.1)	80 (47.2%)	1.06 (0.7 to 1.6)	1.02 (0.3 to 1.6)
Varenicline + placebo (N=171)	60 (40.4%)	1	1	78 (45.7%)	1	1
Week 12						
Varenicline + nicotine patch (N =170)	66 (39.1%)	1.37 (0.8 to 21)	1.24 (0.8 to 2.6)	68 (40.2%)	1.37 (0.8 to 2.1)	1.20 (0.7 to 2.1)
Varenicline + placebo (N=171)	54 (31.8%)	1	1	56 (38.5%)	1	1
Week 24						
Varenicline + nicotine patch (N =170)	56 (32.8%)	1.25 (0.8 to 2.0)	1.17 (0.4 to 1.9)	60 (35.1%)	1.28 (0.8 to 2.0)	1.15 (0.4 to 2.0)
Varenicline + placebo (N=171)	48 (28.2%)	1	1	51 (33.4)	1	1

a. Continuous abstinence from weeks 2 to 8, 12 and 24 weeks
b. Adjusted by age, gender and therapist.

CI, confidence interval; N, number; OR, odds ratio.

Source: Ramon et al, 2014, Table 2

A post hoc exploratory analysis was conducted to assess if the effect of treatment was related to cigarette consumption (≤29 cigarettes per day (cpd) versus >29 cpd); nicotine dependence (Fagerstrom test for nicotine dependence (FTND) score ≤6 versus >6); and previous attempts (none, 1 to 3 and more than 3). The post hoc subgroup analyses revealed that the effect of treatment at 12 and 24 weeks was dependent on cigarette consumption at baseline (interaction P=0.02 at 12 weeks and P = 0.02 at 24 weeks). A non-significant interaction was detected among participants by the level of nicotine dependence (P = 0.06 at 12 weeks and P = 0.1 at 24 weeks) and previous attempts (P = 0.4 at 12 weeks and P = 0.6 at 24 weeks).

Analysis between the subgroups was performed based on the two groups of cigarette smokers, and the rates of continuous abstinence were significantly higher for the combined treatment group than for the control group at week 12 (OR 1.39; 95% CI 1.2 to 2.5) and at week 24 (OR 1.46; 95% CI 1.2 to 2.8) in the subgroup who smoked more than 29 cpd (**Table 22**). In contrast, the differences in the rates among smokers of 29 or fewer cpd were not significant at weeks 8, 12 and 24.

Table 22: Smoking abstinence by group and cigarette consumption

Group	Smokers ≤29 cigarettes per day			Smokers > 29 cigarettes per day		
Continuous abstinence	**Abstainers (%)**	**Crude OR (95% CI)**	**OR[a] (95% CI)**	**Abstainers (%)**	**Crude OR (95% CI)**	**OR[a] (95% CI)**
Week 2 to 8						
Varenicline + nicotine patch	38/78 (48.7%)	1.05 (0.7 to 1.4)	1.0 (0.5 to 1.3)	34/92 (36.9%)	1.13 (0.7 to 1.6)	1.07 (0.6 to 1.8)
Varenicline + placebo	39/84 (46.4%)	1	1	29/87 (33.3%)	1	1
Week 2 to 12						
Varenicline + nicotine patch (N =170)	35/78 (43.6%)	1.14 (0.7 to 1.6)	1.0 (0.5 to 1.8)	31/92 (34.8%)	1.44 (0.9 to 2.3)	1.39 (1.2 to 2.5)
Varenicline + placebo (N=171)	33/84 (39.2%)	1	1	21/87 (24.1%)	1	1
Week 2 to 24						
Varenicline + nicotine patch (N =170)	27/78 (34.6%)	0.99 (0.6 to 1.5)	1.0 (0.7 to 1.6)	29/92 (31.5%)	1.52 (1.0 to 2.5)	1.46 (1.2 to 2.8)
Varenicline + placebo (N=171)	30/84 (35.7%)	1	1	18/87 (20.6%)	1	1

a. Adjusted by age, gender and therapist.

CI, confidence interval; N, number; OR, odds ratio.

Source: Ramon et al, 2014, Table 3

Adverse events

Adverse events occurred in 41.3% of smokers in the combination group compared with 39.7% in the control group (χ^2 value 0.07; P=0.79). The various adverse events that were observed are shown in **Table 23**. Insomnia (χ^2 value 0.85; P=0.35), abnormal dreams (χ^2 value 0.21; P=0.64) and nausea (χ^2 value 0.02; P=0.88) were the most frequently reported events in both groups. Headache was more frequently observed in the nicotine patch group (4.1% versus 2.6), but the differences were not statistically significant when both groups were compared (χ^2 value 0.86; P=0.35). No serious adverse events occurred during follow-up.

Five smokers in the combination group discontinued treatment because of adverse events (three because of nausea and two because of insomnia), and four smokers in the control group discontinued (one because of depressive symptoms, one because of insomnia and two because of nausea).

Table 23: Adverse events

Adverse event	Varenicline + nicotine patch Number = 170 N (%)	Varenicline + placebo Number = 171 N (%)
Insomnia	29 (17.3%)	23 (13.2%)
Nausea	31 (18.3%)	33 (19.1%)
Abnormal dreams	29 (17.4%)	26 (15.1%)
Constipation	15 (8.8%)	13 (7.6%)
Dyspepsia	10 (5.9%)	8 (4.7%)
Headache	7 (4.1%)	4 (2.6%)
Other[a]	9 (5.3%)	11 (6.4%)

a. Irritability, depressive symptoms, fatigue hypotension
Source: Ramon et al, 2014, Table 4

Observational studies

Berg et al, 2017

Abstinence Rates

Note that self-reported quit rates were a secondary outcome measure of this observational study of triple therapy (varenicline, NRT patch and NRT lozenge) in 36 smokers. The self-reported point-prevalence abstinence at Week 12 was 58%, assuming that any withdrawn participants (n = 1) or participants with missing data (n = 9) had returned to smoking. Fourteen participants (38%) reported prolonged abstinence from Week 2 through Week 12.

Ebbert et al, 2009

Abstinence rates

Note that this cohort analysis was based on chart review of 239 smokers enrolled in a tobacco treatment program. All patients who could not be contacted were considered to be continuing smokers. For the combination varenicline and NRT group, we restricted abstinence rates

analyses to the group of patients who had at least 6 months of follow-up (*n* = 93). The 30-day point prevalence smoking abstinence rate for patients receiving varenicline and NRT at 6 months was 54% (95% *CI* = 44% – 64%). For the usual-care group (*N* = 135), the 30-day point prevalence smoking abstinence rate at 6 months was 59% (95% *CI* = 50% – 66%).

Summary of evidence for combination therapy

Of the three combination RCTs, only Koegelenberg *et al* (2014) showed a significantly beneficial effect for the combination of varenicline + NRT. This is likely to be due to the treatment regimen used where NRT was initiated two weeks prior to the TQD and one week prior to varenicline. In Ramon *et al* (2014), where NRT was commenced from the TQD and one week after initiating varenicline, the differences were significant in individuals who smoked >29 cigarettes per day.

Despite the difference in the design of the studies, a meta-analysis of these three RCTs, with endpoints from Hajek *et al* at 4 weeks and Koegelenberg *et al* and Ramon *et al* at 12 weeks, concluded that combination therapy is more effective than varenicline alone, especially if NRT is taken prior to the TQD. Forest plots for the OR, RR and RD of the three studies have been generated and show an overall combined benefit effect (**Figure 13** to **Figure 15**).

Figure 13: Varenicline + NRT vs Varenicline + Placebo: risk difference

Figure 14: Varenicline + NRT vs Varenicline + Placebo: risk ratio

Figure 15: Varenicline + NRT vs Varenicline + Placebo: odds ratio

The observational studies demonstrate that the combination of varenicline + NRT is safe and well-tolerated, with high rates of satisfaction and self-reported quitting.

The adverse event profile of the combination is similar to that of individual agents, however the RCTs reported a numerically greater incidence of nausea, insomnia abnormal dreams, sleep disturbance, skin reactions, constipation, headache and depression with combination therapy versus varenicline monotherapy

Despite the less than favourable results in Hajek *et al* (2013) and in individuals who smoked ≤29 cigarettes in Ramon *et al* (2014), combination therapy should be considered in individuals who have not been successful with varenicline monotherapy and in certain risk groups.

Pfizer is supportive of NACCHO's submission to this review requesting consideration of combination therapy, including varenicline + NRT, for Aboriginal and Torres Strait Islander smokers.

4. Subject to the findings of Terms of Reference 1, 2 and 3, review the cost-effectiveness of medicines for smoking cessation.

Economic evaluations in Pharmaceutical Benefits Advisory Committee (PBAC) submissions for varenicline have consistently shown this smoking cessation agent to be highly cost-effective.

The first major PBAC submission for varenicline was to obtain PBS-listing for initiation and continuation of varenicline and compared varenicline to bupropion, which was Pharmaceutical Benefits Scheme (PBS)-listed for smoking cessation at the time.

The second major PBAC submission for varenicline was for a second 12 weeks of treatment in individuals who had ceased smoking after the initial 12 weeks of treatment. The economic evaluation in this submission compared varenicline to placebo in individuals who had ceased smoking after 12 weeks of treatment.

A third major PBAC submission and a resubmission were to propose that a second course of varenicline be permitted 6 months after the initial course of treatment, instead of being required to wait until the next year. This submission compared varenicline to a combination of placebo, bupropion and NRT in individuals who had previously received a course of varenicline.

The economic evaluations from these PBAC submissions were updated by including the most recent:

- Australian population statistics,
- Australian age-specific death rates,
- Australian smoking rates, and
- PBS costs (2020) for varenicline, bupropion and NRT.

In addition, economic evaluations were performed with the efficacy estimates adjusted to reflect the usage of the smoking cessation treatments in clinical practice i.e. the efficacy estimates were reduced due to discontinuation of treatment and consequent reduction in overall efficacy in these patients. In addition costs were reduced based on usage of smoking cessation agents in clinical practice Finally, estimates for current smoking-related deaths were included.

Further economic evaluations, which had not been included in the original submissions, were performed:

- Varenicline vs NRT, and
- Varenicline + NRT vs NRT.

The updates to previous economic analyses as well as these addition economic analyses show that varenicline remains highly cost-effective in all scenarios. Whether performed using the total treatment costs and evidence from clinical studies or adapted to reflect discontinuation rates seen in clinical practice, varenicline is highly cost-effective with a cost per QALY of <$15,000 for all evaluations except the unadjusted evaluation of a second course of varenicline in individuals who quit after 12 weeks of treatment. In this case the cost per QALY was <$20,000.

Further details of the cost-effectiveness analysis are provided as a separate confidential document.

Conclusion of submission to post-market review of smoking cessation treatments

As noted previously, this submission has focused on varenicline as Pfizer is the applicant for this treatment.

This submission provides evidence that varenicline is extremely effective for smoking cessation as demonstrated in clinical studies performed for registration of this product and many studies performed in a large number of populations since registration. In addition, due to concerns in individuals with mental health issues a number of studies have been performed in these populations and have alleviated these concerns.

Varenicline is used as is outlined in international guidelines and the RACGP guide. These guidelines also recommend the use of varenicline in combination with NRT and this should be considered in individuals who do not achieve smoking cessation on monotherapy.

Finally varenicline continues to be a highly cost-effective treatment both using results of clinical studies and with discontinuation rates seen in clinical practice.

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