



Characterising the use of varenicline: an analysis of the Australian dispensing claims data

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Abstract

Background and aims: In Australia, patterns of use of smoking cessation medications and factors associated with their dispensing are currently not known. This study aimed to measure the demographic and clinical factors associated with varenicline dispensing compared with nicotine replacement therapy (NRT) and bupropion among first-time users of Pharmaceutical Benefits Scheme (PBS) subsidised smoking cessation medicines in Australia and to characterise those who discontinued varenicline treatment prematurely.

Design: Retrospective, population-based study. Logistic regression was used to identify factors associated with varenicline dispensing compared with NRT and bupropion. Sensitivity analyses estimated the proportion of individuals who completed the recommended 12 weeks of varenicline treatment.

Setting and participants: First-time users of PBS subsidised smoking cessation medicines in Australia. Individuals first dispensed a smoking cessation medicine between 2011 and 2019 were identified from a 10% random sample of the national dispensing claims data.

Measurements: The outcome for the regression analysis was the dispensing of varenicline compared with NRT and bupropion. The dispensing of a smoking cessation medicine was identified using the World Health Organization Anatomical Therapeutic Chemical Classification System and PBS item codes. Independent variables included demographic and clinical characteristics such as sex, age, concessional status, year of treatment initiation and comorbidities identified using the Rx-Risk index. The proportion of people who discontinued varenicline treatment after the initiation pack was determined using prescription refill data.

Findings: A total of 94 532 people had their first PBS subsidised smoking cessation medicine. Of these, 62 367 (66.0%) were dispensed varenicline, 29 949 (31.7%) NRT and 2216 (2.3%) bupropion. The odds of varenicline dispensing were higher in males (OR, 1.18; 95% CI, 1.14–1.21), but lower in older adults (0.86 [0.82–0.90] in above 30 years to 0.49 [0.47–0.52] in 61 years and above), among concession beneficiaries (0.44; 0.43–0.46), and those with congestive heart failure (0.60; 0.53–0.68), depression (0.61; 0.54–0.69), anxiety (0.70; 0.66–0.73), psychotic illness (0.39; 0.37–0.42), and chronic obstructive pulmonary disease (0.87; 0.82–0.92). The majority (37 670; 60.4%) of those

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dispensed varenicline discontinued treatment after the initiation pack. Anxiety and psychotic illnesses were significantly more prevalent in those who discontinued treatment. Only 2804 (4.5%) of those dispensed varenicline completed 12 weeks of treatment.

Conclusion: Individuals dispensed varenicline in Australia appear to be healthier compared with those who are dispensed nicotine replacement therapy or bupropion.

KEYWORDS

Bupropion, drug utilization, medication adherence, nicotine dependence, nicotine replacement therapy, pharmacoepidemiology, smoking cessation, varenicline

INTRODUCTION

Smoking is the leading preventable cause of deaths and ill-health worldwide, killing ~7 million people each year [1]. In Australia, tobacco use is the leading cause of cancer and accounts for 22% of the country's cancer burden [2]. Nicotine replacement therapy (NRT), varenicline and bupropion are three evidence-based treatments currently licensed for managing nicotine dependence in Australia. A Cochrane meta-analysis indicated that although single forms of NRT and bupropion showed equal efficacy, varenicline outperformed both agents (vs single forms of NRT: OR, 1.57; 95% CI, 1.29–1.91; vs bupropion: OR, 1.59; 95% CI, 1.29–1.96) and had equal efficacy as combination NRT [3]. The success of smoking cessation pharmacotherapy, however, is largely dependent on adherence to treatment [4]. Studies have found that adherence to varenicline is often suboptimal [5, 6]. Good adherence to varenicline (taking ≥80% of the prescribed regimen) has been associated with a 2-fold increase in 6-month abstinence rates [7].

Since its introduction, numerous studies [8–10] have found significant variabilities in varenicline use, which may be the result of safety concerns raised by the United States Food and Drug Administration (US FDA) [11]. In 2008, the FDA highlighted concerns regarding worsening of an existing psychiatric illness and/or its potential recurrence in patients treated with varenicline [8]. Subsequently, in 2009 the FDA mandated that varenicline carried a 'Black Box Warning' (BBW) alerting healthcare professionals to the possibility of adverse events that included depressed mood, hostility, agitation, suicidal thoughts and attempted suicide [12]. Additionally, in 2011 a safety announcement was issued, which highlighted a small, increased risk of cardiovascular events in smokers with cardiovascular disease, when treated with varenicline [13]. However, because the issue of these warnings several large-scale studies have found no increase in neuropsychiatric adverse events attributable to varenicline relative to nicotine patch or placebo in those with or without pre-existing psychiatric illness [14, 15]. Similarly, no increase in adverse cardiovascular event rates have been found in those treated with varenicline compared with placebo (risk difference, -0.60, 95%CI, -3.35–2.15) [16]. Although the BBW was removed in 2016 as a result of these findings, current literature suggests that concerns may still exist among prescribers and consumers [8–10].

The standard varenicline regimen is 1 mg twice daily for 12 weeks, with the dose titrated up over the first week of

treatment (0.5 mg once daily for 3 days then 0.5 mg twice daily for 4 days then 1 mg twice daily thereafter) and a quit date set at day 14. Studies indicate that an extended duration of varenicline treatment (24 weeks) is more effective in preventing relapse and improving long-term quit rates in those who adhere to the standard treatment [17–19]. A study reported that carbon monoxide (CO) verified 7-day point prevalence abstinence rates at week 24 were significantly higher among adherent individuals who received 24 weeks of treatment versus those who received the standard 12-week treatment (60.5% vs 44.7%, $P=0.04$) [19]. In Australia, the Pharmaceutical Benefits Scheme (PBS) subsidises an initial course (12 weeks) of varenicline treatment, which consists of an initiation pack (4 weeks of treatment) and continuation packs (8 weeks of treatment), for those who are motivated to quit and undergo concurrent counselling for smoking cessation through a comprehensive support and counselling program. An additional 12 weeks of treatment is available for those who quit smoking in the process of completing the initial 12-week course or following an initial 12-week course of varenicline [20]. However, details of the counselling support received (if any) by patients undergoing varenicline treatment are not available in the PBS dataset.

Little was known about the factors associated with varenicline dispensing and treatment discontinuation among first-time users of PBS subsidised smoking cessation treatment. Therefore, the aim of this study was to evaluate the initial treatment decisions for patients who consult with physicians about smoking cessation pharmacotherapy in Australia. The specific objectives of the study were to: (i) assess the demographic and clinical factors associated with varenicline dispensing compared with NRT and bupropion among first-time users of PBS subsidised smoking cessation treatment in Australia; (ii) examine the pattern of varenicline use by comparing and contrasting the characteristics of those who discontinued treatment after the initiation pack versus those who continued treatment; (iii) and estimate the proportion of people who completed 12 weeks of varenicline treatment.

When evaluating the factors associated with varenicline dispensing compared with NRT and bupropion, it is imperative to note that NRT is also available from supermarkets and over-the-counter (OTC) in Australia, albeit at a higher cost to the individual. The use of NRT on the PBS represented only 7% of the overall use in Australia in 2019, suggesting that the majority of NRT products are purchased OTC [21]. However, the use of NRT OTC is outside the scope of this analysis as these data are not captured in the PBS dataset.

Nonetheless, the aim of this analysis is to evaluate the initial treatment decisions for patients who consult with physicians about smoking cessation pharmacotherapies in Australia. Therefore, smokers who purchase NRT OTC are unlikely to be representative of patients who present to primary care for smoking cessation advice and as such are likely to be an inappropriate control group for patients prescribed varenicline.

METHODS

Study design, data source and study population

This retrospective, population-based study used data from a 10% random sample of Australia's PBS, a national program that subsidises the cost of prescription medicines [22]. The PBS data are available for researchers in a number of different extracts or formats [23]. The 10% PBS sample is one of these extracts and is a longitudinal, standardised, unit-record dataset that contains all PBS medicine dispensing information for a random 10% sample of Australians [23]. Access to this dataset was established through a contract with Services Australia (formerly Department of Human Services) [23]. Monash University has a licence agreement to access this dataset for research.

NRT has been subsidised on the PBS to the general Australian population since February 2011. Before this, NRT was subsidised on the PBS only for veterans and the Aboriginal and Torres Strait Islander population. NRT is also available from supermarkets and OTC in Australia, but at a higher cost to individuals than through the PBS. The majority of NRT products are purchased from supermarkets or OTC; however, the use of non-prescription NRT is outside the scope of this analysis because this information is not captured in the PBS dataset. Bupropion was listed on the PBS in August 2000 and varenicline in January 2008. The additional 12 weeks of varenicline treatment has been subsidised through the PBS from 1 February 2011.

The study population included adults ages 18 to 99 years dispensed NRT, bupropion or varenicline. Dispensed medications were identified by using the relevant World Health Organization (WHO) Anatomical Therapeutic Chemical Classification System (ATC) and PBS item codes (Supporting information Data S1). Varenicline is prescribed in Australia as per the PBS requirements shown in Supporting information Data S2.

Cohort definition

We included first-time users of PBS subsidised smoking cessation medication that were defined as individuals with their first dispensing of a smoking cessation medicine (NRT, bupropion or varenicline) between 1 January 2011 and 31 December 2019, with no previous dispensing of a smoking cessation medication since 2007. The above time period has been chosen to capture PBS dispensing data on all

three pharmacotherapies, including the additional 12 weeks of subsidised treatment of varenicline.

Factors associated with varenicline dispensing

Factors associated with varenicline dispensing were compared with the dispensing of NRT and bupropion. A validated comorbidity index (Rx-Risk index) was used to identify comorbidities based on medications dispensed in the year before or on the index date of supply [24].

Specific comorbidities and the supply of other cardiovascular-related pharmacotherapies (antiplatelets and anticoagulants) were considered using the Rx-Risk index (Supporting information Data S1). Comorbidities included anxiety, depression, congestive heart failure (CHF), ischaemic heart disease, hypertension, hyperlipidaemia and chronic obstructive pulmonary disease (COPD). Demographic information included age, sex and concessional status. Concessional beneficiaries pay a smaller co-payment than general beneficiaries for prescription medicines. For the purposes of this study, concessional beneficiaries consisted of people with a Pension Card, Commonwealth Seniors Card, Health Care Card or a Safety Net Card.

Pattern of varenicline use

Of those who had an index varenicline dispensing (first dispensing of an initiation pack), we determined the proportion of people who were dispensed a continuation pack within 60 days of the index supply being exhausted (Figure 1). Discontinuation of treatment after the initiation pack was defined as more than 60 consecutive days between the index varenicline dispensing and the continuation pack dispensing, during which an individual had no varenicline available (Figure 1). Of the people who discontinued treatment after the initiation pack, we estimated the proportion of people who were dispensed NRT or bupropion within 12 months of the index varenicline dispensing to estimate the proportion who may have switched smoking cessation pharmacotherapy.

Sensitivity analyses were performed using prescription refill status to estimate the proportion of people who completed the initial 12 weeks of varenicline treatment and remained abstinent, by estimating the proportion of people who were dispensed an additional 12-week supply of varenicline within 60 days of the previous supply being exhausted (Figure 1).

MEASURES

Independent variables

The predictors included in the analysis were demographic and clinical characteristics such as sex, age, concessional status, year of treatment

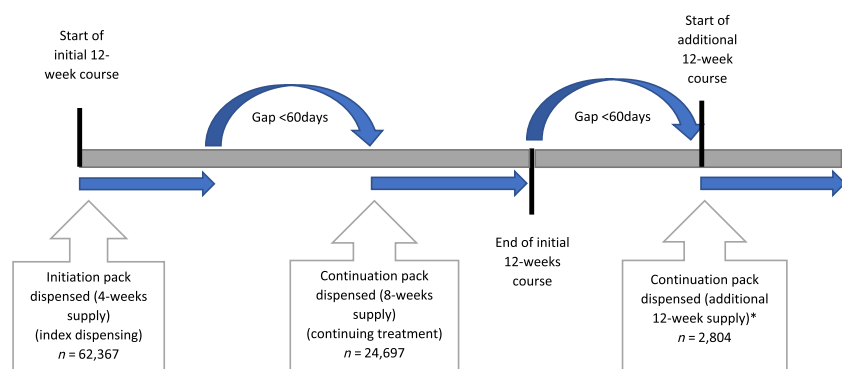


FIGURE 1 Pattern of varenicline use among those with an index dispensing in 2011 to 2019. *n*: number of participants. *PBS criterion for the additional 12-week supply: patient must have ceased smoking in the process of completing an initial 12 weeks or ceased smoking following an initial 12 weeks of PBS-subsidised treatment with this drug in the current course of treatment. PBS = Pharmaceutical Benefits Scheme

initiation and comorbidities identified using the Rx-Risk index (Supporting information Data S1).

Dependent variables

The outcome for the regression analysis was the dispensing of varenicline compared with NRT and bupropion. The dispensing of a smoking cessation medicine was identified using the WHO ATC and PBS item codes (Supporting information Data S1).

Statistical analysis

Baseline characteristics were presented as means with SD or as frequencies and percentages. Using multivariable logistic regression models, adjusted ORs and 95% CI were estimated for factors associated with varenicline dispensing compared with the dispensing of NRT or bupropion. A purposeful selection approach was used to identify the variables for the multivariable analysis [25]. Variables that had a *P* value of <0.25 in univariate analysis were included in the multivariable analyses along with the variables known to be clinically important. Variables were included in the final regression model, if they were significantly related to the outcome variable at the 0.1 α level. Demographic and clinical factors associated with the discontinuation of treatment after the initiation pack and the dispensing of an additional 12-week supply were also presented. Missing data were treated as unknown. All analyses were conducted using the statistical package SAS version 9.4 (SAS Institute). A *P* < 0.05 was subsequently regarded as statistically significant.

The analysis plan for this study was not pre-registered and our findings should be considered exploratory.

Institutional review and data approval

This study was approved by the Monash University Human Research Ethics Committee (ID 22877). The analysis approval was obtained from and the final manuscript was noted by Services Australia's External Request Evaluation Committee (EREC number RMS1662).

RESULTS

We found that a total of 94 532 people (mean age 43.5 ± 14.9 years) had their first dispensing of a PBS subsidised smoking cessation medicine between 2011 and 2019 (Table 1). Of these, ~66.0% (*n* = 62 367) were dispensed varenicline, 31.7% (*n* = 29 949) NRT and 2.3% (*n* = 2216) bupropion. People dispensed NRT were significantly older (47.9 ± 15.8 years) compared with those dispensed varenicline (41.4 ± 13.9 years) or bupropion (41.9 ± 14.0 years) (Table 1). Men accounted for 59.0% (*n* = 36 777), 50.7% (*n* = 15 172), and 51.1% (*n* = 1132) of those dispensed varenicline, NRT and bupropion, respectively.

Demographic and clinical factors associated with varenicline dispensing vs. NRT and bupropion

Male gender was associated with increased odds of being dispensed varenicline compared with NRT or bupropion (1.18 [1.14–1.21]) (Table 2). Increasing age was associated with decreasing odds of being dispensed varenicline compared with those ages 18 to 30 years (Table 2). Similarly, concessional beneficiaries had lower odds of being dispensed varenicline compared with general beneficiaries (0.44 [0.43–0.46]).

People with CHF (0.60 [0.53–0.68]), ischaemic heart disease/angina (0.73 [0.65–0.83]), ischaemic heart disease/hypertension (0.90 [0.85–0.95]), depression (0.61 [0.54–0.69]), anxiety (0.70 [0.66–0.73]), bipolar disorder (0.53 [0.44–0.65]), psychotic illness (0.39 [0.37–0.42]), alcohol dependency (0.56 [0.47–0.66]), epilepsy (0.68 [0.62–0.74]) and COPD (0.87 [0.82–0.92]) had lower odds of being dispensed varenicline compared with NRT or bupropion (Table 2).

Pattern of varenicline use

Of the individuals dispensed a varenicline initiation pack (*n* = 62 367), only 24 697 (39.6%) were dispensed a continuation pack (continued treatment) suggesting that the majority (60.4%) discontinued treatment after the initiation pack (4 weeks of treatment or less) (Figure 1). Of those who discontinued treatment after the initiation pack, 1399

TABLE 1 Demographic and clinical characteristics of individuals first dispensed a smoking cessation medicine between 2011 and 2019

	Total (n = 94 532)	Varenicline (n = 62 367)	NRT (n = 29 949)	Bupropion (n = 2216)
Age, y, mean (\pm SD)	43.5 \pm 14.9	41.4 \pm 13.9	47.9 \pm 15.8	41.9 \pm 14.0
Sex, male, n (%)	53 081 (56.2)	36 777 (59.0)	15 172 (50.7)	1132 (51.1)
Concession beneficiaries, n (%) ^{a,c}	42 972 (46.0)	22 059 (35.6)	20 017 (68.4)	896 (40.8)
Comorbidity score median (IQR) ^b	1.0 (0.0–3.0)	1.0 (0.0–2.0)	2.0 (1.0–4.0)	1.0 (0.0–3.0)
No. comorbidities, n (%) ^b				
0	33 778 (35.7)	27 531 (44.1)	5614 (18.7)	633 (28.5)
1–3	41 672 (44.1)	26 762 (42.9)	13 823 (46.2)	1087 (49.1)
4–6	14 091 (14.9)	6355 (10.2)	7361 (24.6)	375 (16.9)
7+	4991 (5.3)	1719 (2.8)	3151 (10.5)	121 (5.5)
Antiplatelet therapy n (%)	1914 (2.0)	742 (1.2)	1137 (3.8)	35 (1.6)
Anticoagulant therapy n (%)	4113 (4.4)	1573 (2.5)	2486 (8.3)	54 (2.4)
Hyperlipidaemia n (%)	13 888 (14.7)	6935 (11.1)	6679 (22.3)	274 (12.4)
Hypertension n (%)	13 012 (13.8)	6381 (10.2)	6355 (21.2)	276 (12.5)
Congestive heart failure n (%)	1479 (1.6)	473 (0.8)	983 (3.3)	23 (1.0)
Arrhythmia n (%)	675 (0.7)	239 (0.4)	430 (1.4)	6 (0.3)
Ischaemic heart disease/angina n (%)	1735 (1.8)	628 (1.0)	1086 (3.6)	21 (1.0)
Ischaemic heart disease/hypertension	8627 (9.1)	4016 (6.4)	4411 (14.7)	200 (9.0)
Depression n (%)	22 557 (23.9)	10 893 (17.5)	10 832 (36.2)	832 (37.6)
Anxiety n (%)	10 255 (10.9)	4352 (7.0)	5547 (18.5)	356 (16.1)
Bipolar disorder n (%)	646 (0.7)	158 (0.3)	437 (1.5)	51 (2.3)
Psychotic illness n (%)	6538 (6.9)	1987 (3.2)	4295 (14.3)	256 (11.6)
Alcohol dependency n (%)	738 (0.8)	270 (0.4)	417 (1.4)	51 (2.3)
Epilepsy n (%)	3221 (3.4)	1140 (1.8)	1986 (6.6)	95 (4.3)
Chronic obstructive pulmonary disease n (%)	8268 (8.8)	4004 (6.4)	4099 (13.7)	165 (7.5)

Abbreviation: NRT = nicotine replacement therapy.

^aConcession beneficiaries pay a smaller co-payment than general beneficiaries. Concession beneficiaries consist of people with a Pensioner, Commonwealth Seniors Card, Health Care Card or Safety Net Card.

^bA score of 1 was deducted from the total Rx-Risk score of individuals, because the whole cohort had a medication dispensed for smoking cessation at baseline.

^cMissing n = 1119.

(3.7%) switched to NRT or bupropion within 12 months of the index varenicline dispensing.

Characteristics of people who discontinued varenicline after the initiation pack vs. those who continued

Characteristics of those who discontinued treatment after the initiation pack are presented in Table 3. Hyperlipidaemia ($P < 0.001$), ischaemic heart disease/angina ($P = 0.0164$), ischaemic heart disease/hypertension ($P < 0.001$) and COPD ($P = 0.027$) were significantly more prevalent in those who continued treatment, compared with those who discontinued after the initiation pack (Table 3). In contrast to this, the prevalence of anxiety ($P < 0.001$) and psychotic illnesses ($P = 0.003$) was significantly lower in those who continued varenicline treatment (Table 3).

Proportion of people who completed 12-weeks of varenicline

Sensitivity analysis indicated that of the total varenicline cohort ($n = 62\,367$), only 2804 (4.5%) people were dispensed an additional 12-week supply and hence, were deemed to have completed the initial 12-week course and were likely to have remained abstinent (Figure 1). Characteristics of people who continued treatment after the initiation pack and were dispensed an additional 12-week supply of varenicline versus those who were not dispensed an additional supply are presented in Table 4. Hyperlipidaemia ($P < 0.001$), hypertension ($P < 0.001$), COPD ($P < 0.001$), depression ($P < 0.001$), anxiety ($P < 0.001$) and psychotic illnesses ($P < 0.001$) were significantly more prevalent in those who were dispensed an additional 12-week supply (Table 4).

TABLE 2 Factors associated with the dispensing of varenicline compared with NRT or bupropion among first-time users of PBS subsidised smoking cessation medicine in 2011–2019

	<i>Unadjusted OR (95% CI)</i>	<i>Unadjusted P value</i>	<i>Adjusted OR (95% CI)</i>	<i>Adjusted P value</i>
Sex, male	1.40 (1.36–1.44)	<0.001	1.18 (1.14–1.21)	<0.001
Age, y				
18–30	Reference		Reference	
31–40	0.82 (0.79–0.86)		0.86 (0.82–0.90)	
41–50	0.66 (0.63–0.68)		0.72 (0.69–0.76)	
51–60	0.51 (0.48–0.53)		0.60 (0.57–0.63)	
61+	0.29 (0.28–0.31)	<0.001	0.49 (0.47–0.52)	<0.001
Concession beneficiary ^{a,c}	0.28 (0.27–0.29)	<0.001	0.44 (0.43–0.46)	<0.001
Year of initiation				
2011–2013	Reference		Reference	
2014–2016	0.95 (0.92–0.98)		1.04 (1.00–1.08)	
2017–2019	0.65 (0.62–0.67)	<0.001	0.70 (0.68–0.73)	<0.001
Number of comorbidities ^b				
0	Reference		Reference	
1–3	0.41 (0.39–0.42)		0.74 (0.71–0.77)	
4–6	0.19 (0.18–0.20)		0.74 (0.69–0.79)	
7+	0.12 (0.11–0.13)	<0.001	0.91 (0.81–1.01)	<0.001
Antiplatelet therapy	0.30 (0.28–0.32)	<0.001	0.65 (0.60–0.71)	<0.001
Anticoagulant therapy	0.32 (0.29–0.35)	<0.001	0.61 (0.55–0.68)	<0.001
Arrhythmias	0.28 (0.24–0.33)	<0.001	–	–
Hypertension	0.44 (0.42–0.46)	<0.001	0.96 (0.91–1.01)	0.093
Congestive heart failure	0.24 (0.21–0.26)	<0.001	0.60 (0.53–0.68)	<0.001
Ischaemic heart disease/angina	0.29 (0.26–0.32)	<0.001	0.73 (0.65–0.83)	<0.001
Ischaemic heart disease/hypertension	0.41 (0.39–0.43)	<0.001	0.90 (0.85–0.95)	<0.001
Depression	0.37 (0.36–0.38)	<0.001	0.61 (0.54–0.69)	<0.001
Anxiety	0.33 (0.32–0.35)	<0.001	0.70 (0.66–0.73)	<0.001
Bipolar disorder	0.17 (0.14–0.20)	<0.001	0.53 (0.44–0.65)	<0.001
Psychotic illness	0.20 (0.19–0.21)	<0.001	0.39 (0.37–0.42)	<0.001
Alcohol dependency	0.30 (0.25–0.34)	<0.001	0.56 (0.47–0.66)	<0.001
Epilepsy	0.27 (0.25–0.29)	<0.001	0.68 (0.62–0.74)	<0.001
Chronic obstructive pulmonary disease	0.45 (0.43–0.47)	<0.001	0.87 (0.82–0.92)	<0.001

^aConcession beneficiaries pay a smaller co-payment than general beneficiaries. Concession beneficiaries consist of people with a Pensioner, Commonwealth Seniors Card, Health Care Card or Safety Net Card.

^bA score of 1 was deducted from the total Rx-Risk score of individuals, because the whole cohort had a medication dispensed for smoking cessation at baseline.

^cMissing $n = 1119$.

DISCUSSION

Our results indicated that among first-time users of PBS subsidised smoking cessation medicines in Australia, varenicline is the most commonly dispensed medicine, followed by NRT. Compared with NRT or bupropion, varenicline dispensing was less likely among women, older individuals and those with comorbidities such as anxiety, depression, bipolar disorder, psychotic illnesses, alcohol dependency, CHF and COPD. Furthermore, our findings indicated that the majority (60.4%) of individuals dispensed varenicline, discontinued treatment after the

initiation pack (4 weeks of treatment or less). Those who continued varenicline treatment after the initiation pack had a significantly higher prevalence of ischaemic heart disease/angina, ischaemic heart disease/hypertension and COPD, but a lower prevalence of anxiety and psychotic illnesses compared with those who discontinued treatment. Of those who discontinued treatment, only 3.7% switched to NRT or bupropion within 12 months of the index varenicline dispensing. Furthermore, our study showed that of the people dispensed varenicline, only 4.5% were likely to have completed 12 weeks of treatment and achieved abstinence. Further research is needed to

TABLE 3 Characteristics of people who discontinued treatment after the initiation pack versus those who continued treatment

	<i>Discontinued treatment (n = 37 670)</i>	<i>Continued treatment (n = 24 697)</i>	<i>Unadjusted OR (95% CI)^d</i>	<i>P-value</i>
Sex, male	22 185 (58.9)	14 592 (59.1)	1.01 (0.98–1.04)	0.635
Age, y				
18–30	11 737 (31.2)	4988 (20.2)	Reference	
31–40	9003 (23.9)	5973 (24.2)	1.56 (1.49–1.64)	
41–50	7918 (21.0)	5992 (24.3)	1.78 (1.70–1.87)	
51–60	5588 (14.8)	4689 (19.0)	1.97 (1.87–2.08)	
61+	3424 (9.1)	3055 (12.4)	2.10 (1.98–2.23)	<0.001
Concession beneficiary ^{a,c}	13 711 (36.6)	8348 (34.1)	0.90 (0.87–0.93)	<0.001
Year of initiation				
2011–2013	19 846 (51.7)	13 381 (54.2)	Reference	
2014–2016	10 442 (27.7)	7069 (28.6)	0.99 (0.95–1.02)	
2017–2019	7742 (20.6)	4247 (17.2)	0.80 (0.77–0.83)	<0.001
No. of comorbidities ^b				
0	16 658 (44.2)	10 873 (44.0)	Reference	
1–3	16 352 (43.4)	10 410 (42.2)	0.98 (0.94–1.01)	
4–6	3716 (9.9)	2639 (10.7)	1.09 (1.03–1.15)	
7+	944 (2.5)	775 (3.1)	1.26 (1.14–1.39)	<0.001
Antiplatelet therapy	895 (2.4)	678 (2.8)	1.16 (1.05–1.28)	0.004
Anticoagulant therapy	407 (1.1)	335 (1.4)	1.26 (1.09–1.46)	0.002
Hyperlipidaemia	3745 (9.9)	3190 (12.9)	1.34 (1.28–1.41)	<0.001
Hypertension	3529 (9.4)	2852 (11.6)	1.26 (1.20–1.33)	<0.001
Congestive heart failure	267 (0.7)	206 (0.8)	1.18 (0.98–1.41)	0.078
Arrhythmia	136 (0.4)	103 (0.4)	1.16 (0.90–1.50)	0.262
Ischaemic heart disease/angina	350 (0.9)	278 (1.1)	1.21 (1.04–1.42)	0.016
Ischaemic heart disease/hypertension	2238 (5.9)	1778 (7.2)	1.23 (1.15–1.31)	<0.001
Depression	6636 (17.6)	4257 (17.2)	0.97 (0.93–1.02)	0.223
Anxiety	2740 (7.3)	1612 (6.5)	0.89 (0.84–0.95)	<0.001
Bipolar disorder	98 (0.3)	60 (0.2)	0.93 (0.68–1.29)	0.678
Psychotic illness	1263 (3.4)	724 (2.9)	0.87 (0.79–0.96)	0.003
Alcohol dependency	174 (0.5)	96 (0.4)	0.84 (0.66–1.08)	0.174
Epilepsy	680 (1.8)	460 (1.9)	1.03 (0.92–1.16)	0.601
Chronic obstructive pulmonary disease	2352 (6.2)	1652 (6.7)	1.08 (1.01–1.15)	0.027

^aConcession beneficiaries pay a smaller co-payment than general beneficiaries. Concession beneficiaries consist of people with a Pensioner, Commonwealth Seniors Card, Health Care Card or Safety Net Card.

^bA score of 1 was deducted from the total Rx-Risk score of individuals, because the whole cohort had a medication dispensed for smoking cessation at baseline.

^cMissing $n = 435$.

^dDiscontinued treatment used as a reference category.

identify reasons for early discontinuation of varenicline and interventions that may increase treatment retention, particularly after the completion of the initiation pack.

Our study found that the average age at which individuals were first dispensed a PBS subsidized smoking cessation treatment in Australia was ~43.5 years. Considering that the average age at which individuals have their first full cigarette is 16.6 years [2], this may indicate a reluctance to seek smoking cessation assistance from a

General Practitioner (GP), a lack of perceived need for prescription medicines to assist in the quitting process or lack of quit support offered by the GP at routine visits. Coinciding with this notion are the findings of Watkins et al. who reported that young adult smokers were less likely to use pharmacotherapy and were more likely to quit unassisted compared to older adult smokers [26]. However, despite differences in smoking cessation strategies used, young adults were just as likely to have successfully quit in the short-term as older

TABLE 4 Characteristics of people who were dispensed an additional 12-week supply

	Additional 12-week supply dispensed (n = 2804)	Additional 12-week supply not dispensed (n = 21 893)	Unadjusted OR (95%CI) ^d	Unadjusted P-value
Sex, male	1592 (56.8)	13 000 (59.4)	0.90 (0.83–0.97)	0.0083
Age, y				
18–30	242 (8.6)	4746 (21.7)	Reference	
31–40	528 (18.8)	5445 (24.9)	1.90 (1.63–2.22)	
41–50	724 (25.8)	5268 (24.1)	2.69 (2.32–2.13)	
51–60	751 (26.8)	3938 (18.0)	3.74 (3.22–4.35)	
61+	559 (19.9)	2496 (11.4)	4.39 (3.75–5.14)	<0.001
Concession beneficiary ^{a,c}	1167 (41.6)	7181 (32.8)	1.49 (1.37–1.61)	<0.001
Year of initiation				
2011–2013	1329 (47.4)	12 052 (55.1)	Reference	
2014–2016	833 (29.7)	6236 (28.5)	1.21 (1.11–1.33)	
2017–2019	642 (11.4)	3605 (16.5)	1.62 (1.46–1.79)	<0.001
No. of comorbidities ^b				
0	889 (31.7)	9984 (45.6)	Reference	
1–3	1215 (43.3)	9195 (42.0)	1.48 (1.36–1.63)	
4–6	510 (18.2)	2129 (9.7)	2.69 (2.39–3.03)	
7+	190 (6.8)	585 (2.7)	3.65 (3.06–4.36)	<0.001
Antiplatelet therapy	59 (2.1)	276 (1.3)	1.80 (1.48–2.20)	<0.001
Anticoagulant therapy	125 (4.5)	553 (2.5)	1.68 (1.27–2.24)	<0.001
Hyperlipidaemia	596 (21.3)	2594 (11.8)	2.01 (1.82–2.22)	<0.001
Hypertension	565 (20.1)	2287 (10.4)	2.16 (1.95–2.40)	<0.001
Congestive heart failure	39 (1.4)	167 (0.8)	1.84 (1.30–2.61)	<0.001
Arrhythmia	32 (1.1)	71 (0.3)	3.55 (2.33–5.40)	<0.001
Ischaemic heart disease/angina	48 (1.7)	230 (1.1)	1.64 (1.20–2.25)	0.002
Ischaemic heart disease/hypertension	346 (12.3)	1432 (6.5)	2.01 (1.78–2.28)	<0.001
Depression	717 (25.6)	3540 (16.2)	1.78 (1.62–1.95)	<0.001
Anxiety	270 (9.6)	1342 (6.1)	1.63 (1.42–1.87)	<0.001
Bipolar disorder	14 (0.5)	46 (0.2)	2.38 (1.31–4.34)	0.005
Psychotic illness	145 (5.2)	579 (2.6)	2.01 (1.67–2.42)	<0.001
Alcohol dependency	24 (0.9)	72 (0.3)	2.62 (1.65–4.16)	<0.001
Epilepsy	88 (3.1)	372 (1.7)	1.87 (1.48–2.37)	<0.001
Chronic obstructive pulmonary disease	285 (10.2)	1367 (6.2)	1.70 (1.49–1.94)	<0.001

^aConcession beneficiaries pay a smaller co-payment than general beneficiaries. Concession beneficiaries consist of people with a Pensioner, Commonwealth Seniors Card, Health Care Card or Safety Net Card.

^bA score of 1 was deducted from the total Rx-Risk score of individuals, because the whole cohort had a medication dispensed for smoking cessation at baseline.

^cMissing n = 203.

^dAdditional 12-week supply not dispensed used as reference.

adults and none of the strategies examined were significantly associated with successful abstinence for young adults [26]. Our findings are also in accordance with Clark *et al.* [27] who found that the influence of a medical provider and perceived health effects of smoking were important determinants of readiness to quit in smokers ages 30 to 49 years. Additionally, although smokers ages 18 to 29 years had attitudes and smoking behaviours most favourable to

being ready to quit, no significant predictors of readiness to quit were found [27]. Therefore, further research is needed to explore the avenues, through which smokers attempt quitting in the years leading up to their first dispensing of a PBS subsidised smoking cessation medicine in Australia. Moreover, interventions that assist young adult smokers to achieve long-term abstinence need to be identified.

Our findings are consistent with a British study that analysed primary care databases containing records from over 500 general practices, which found that in 2011 varenicline prescriptions were less likely among older individuals and those with mental health conditions, epilepsy, atrial fibrillation and hypertension [28]. This may be the impact of safety warnings issued by the FDA as a recent study indicates a significant decrease in varenicline use in the years following the 2008 public health advisory [29]. Similar studies have also noted a significant decrease in varenicline use after the FDA mandated BBW in 2009 [8]. Moreover, a study reported that the average predicted probability of cardiovascular disease among US Medicare beneficiaries filling varenicline prescriptions decreased by 31% from 2007 to 2012 [9]. Although recent data suggests that the use of varenicline increased following the publication of the EAGLES study, which showed no increased risk of neuropsychiatric or cardiovascular adverse events in patients treated with varenicline relative to NRT, further research is needed to evaluate the lower likelihood of varenicline dispensing among smokers with certain comorbidities found in our study [14, 16, 29, 30]. Future studies may also need to consider evaluating the perceptions of varenicline among prescribers and patients to identify potential barriers for its use.

Several studies have found that compared to men, women are less successful in quitting smoking and have more difficulty in sustaining abstinence [31, 32]. Augmenting the sex disparity in quitting are findings that suggest differential efficacy of smoking cessation medicines across women and men. Current data suggests that women may be less responsive to NRT and findings for sex differences in bupropion efficacy have been mixed [33, 34]. However, results of a recent meta-analysis of varenicline found significantly higher 7-day point prevalence abstinence rates in women compared to men at the end of treatment and similar rates of abstinence at 1 year [35]. Therefore, further research may be needed to explore the reasons for sex disparities in the dispensing of varenicline among first time users of PBS subsidised smoking cessation medicines in Australia.

These results, however, should be interpreted with caution because of the availability of NRT without a prescription in Australia [21]. The cost of a full 12-week course of nicotine 14 mg/24 hour patches, if purchased OTC, is currently AUD 174.45, whereas the subsidised cost under the PBS is AUD 123.90 for general beneficiaries and AUD 19.80 for concession beneficiaries [36]. Given that the use of prescription medicine is highly sensitive to out-of-pocket costs, the larger cost differential for concession beneficiaries may explain their over-representation in those dispensed NRT in our dataset [37]. These individuals may also have a higher incidence of chronic conditions because they represent a population with higher healthcare use. Nonetheless, this analysis aimed to evaluate the initial treatment decisions for patients who consulted physicians about smoking cessation pharmacotherapies in Australia. As a result, smokers who purchased NRT without a prescription may not be representative of patients who seek physician advice for smoking cessation and are therefore, unlikely to be an appropriate control group for patients dispensed varenicline through the PBS. However, further research is needed to confirm our findings.

In the Comprehensive Medication Program and Support Services (COMPASS) trial, more than half the participants who reported good adherence to varenicline ($\geq 80\%$ of the prescribed regimen) were abstinent at 6 months compared with 25.4% who reported poor adherence [7]. Premature discontinuation of varenicline treatment continues to be a challenge [6, 38]. Findings of the International Tobacco Control (ITC) Four-Country Survey waves 5 and 6 showed that of those who reported using varenicline for quit attempts in the previous year, 59.6% discontinued treatment prematurely, which is similar to that found in our study [38]. The most commonly cited reasons for treatment discontinuation were side effects from the medication, reported by over a third of those who used varenicline or bupropion, belief that the medication was no longer needed and relapse back to smoking [38]. We found that 3.7% of those who discontinued treatment after the initiation pack switched to NRT or bupropion within 12 months of the index varenicline dispensing. This may be because this small group of smokers may have experienced adverse events from varenicline use and therefore, switched smoking cessation pharmacotherapy or it may also be the result of a change in quit strategy across multiple quit attempts. However, further research is needed to determine the reasons for premature discontinuation of varenicline in Australia.

Our findings showed that cardiovascular conditions and COPD were less prevalent in those who discontinued treatment, which may be because of a higher level of perceived vulnerability in these individuals and therefore, a stronger motivation to quit. Conversely, anxiety and psychotic illnesses were more prevalent in those who discontinued treatment. This may be because withdrawal symptoms and cravings may be more severe in these groups of smokers, because of their higher level of nicotine dependence [39]. Additional smoking cessation support to such smokers may increase their likelihood of subsequent prescription refills and ensure that any barriers to quitting are identified and addressed. Using a combination of acute-dose NRT (such as nicotine lozenges) with varenicline may help such smokers to better manage their cravings and withdrawal symptoms, which are particularly common in the first 4 weeks of treatment [40, 41].

The results of our sensitivity analyses indicated that of the people dispensed varenicline; only 4.5% completed 12 weeks of treatment and were likely to have achieved abstinence, which is lower than previously reported [5]. Our results were likely to have underestimated the proportion of people completing 12 weeks of varenicline treatment and who achieved abstinence. It may be possible that some individuals who completed the first 12-week course were not dispensed an additional supply because of a perceived lack of need by the prescriber or the individual, if abstinence had already been achieved with the initial course of treatment. It is also likely that some individuals did complete the initial 12-week course, but did not achieve abstinence and therefore, did not qualify for the subsidised additional supply. In a retrospective, claims-based study of Medicare beneficiaries in the United States, 15% of beneficiaries were reported to be adherent ($\geq 80\%$ of the prescribed regimen) to the 12-week regimen [5]. Adherence in this study was measured using the proportion of days covered, whereas our study relied on the dispensing of an additional 12-week supply as marker for the completion of the initial course of

treatment. Therefore, further research is needed to confirm our findings.

Strengths and limitations

We analysed a large, nationally representative random sample of Australia's PBS beneficiaries. The sampling methodology of the 10% PBS dataset has been confirmed by the Australian Bureau of Statistics, which increases the generalisability of our findings. Therefore, our results have implications for countries that provide universal access to subsidised prescription medications for smoking cessation. By restricting our cohort to the first dispensing of a smoking cessation medicine, we were able to ascertain the demographic and clinical factors associated with dispensing varenicline, whereas excluding the influence of previous experiences with a particular medication (e.g. side effects and impact on the type of medication dispensed subsequently).

However, as is typical of medication claims-based research, we were unable to ascertain whether individuals actually used the dispensed medication as intended. All available variables were included as covariates in our analyses. We could not examine the impact of other sociodemographic factors (such as the level of educational attainment or annual household income) and tobacco use behaviours (such as the level of nicotine dependence or the number of cigarettes per day) on adherence to treatment, because these data were not captured in the PBS dataset. Further research is needed to evaluate the impact of unmeasured variables on the use of smoking cessation medications. In Australia, NRT is also available through supermarkets and OTC, and some forms of NRT are not subsidised by the PBS, which may have had an impact on our results. Although the cost of OTC NRT products is considerably higher than subsidised through the PBS, some people may wish to buy NRT OTC for convenience and/or avoid having discussions about their smoking with their GP or pharmacist. Therefore, a limitation of our study is that it underestimates the use of NRT in Australia because it does not capture the use of OTC NRT products. Use of other non-evidence-based forms of smoking cessation treatment (e.g. acupuncture, hypnotherapy) were also not captured. We were also unable to determine the geographical patterns of varenicline dispensing within Australia because this information was not available. Further research is needed in this area.

Additionally, we were unable to determine whether individuals discontinued varenicline because of successful smoking cessation (during or after the initiation pack or after the initial 12-week course), adverse events or primary non-adherence [42]. The PBS dataset does not contain details of the counselling support (if any) received by patients undergoing varenicline treatment. Therefore, in instances where the continuation packs were not dispensed, we were unable to ascertain whether this was because subsidy criteria were not met (i.e. if they did not undergo concurrent counselling during treatment with the initiation pack) or because a prescription had been issued, but not dispensed. Our results were also likely to underestimate the

proportion of people who completed 12 weeks of varenicline and/or achieved abstinence because of the lack of data on smoking status. Further research is needed to evaluate the reasons for premature discontinuation of varenicline treatment and to corroborate our findings. We were also unable to evaluate the association between different care settings or prescriber speciality and treatment retention. Future research could compare and contrast abstinence outcomes, adherence rates and factors associated with treatment discontinuation among smokers who are initiated on varenicline by GPs compared with hospital specialists.

CONCLUSION

Varenicline was the most commonly dispensed medication among first-time users of PBS subsidised smoking cessation pharmacotherapy in Australia. Varenicline dispensing compared with NRT or bupropion was less likely among older individuals and those with anxiety, depression, bipolar disorder, psychotic illnesses, alcohol dependency, CHF and COPD. Approximately 60% of those dispensed varenicline discontinued treatment after the initiation pack and <5% completed the initial 12-week course and were likely to have achieved abstinence. The prevalence of anxiety and psychotic illnesses was higher among those who discontinued treatment compared with those who continued treatment after the initiation pack.

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DECLARATION OF INTERESTS

M.J.A., B.B. and J.G. hold an investigator-initiated grant from Pfizer (which manufactures and markets varenicline) for a clinical trial of varenicline in hospital patients, and for unrelated research from Boehringer-Ingelheim and from GSK (which manufactures and markets bupropion). J.G. has received honoraria through consultations for Pfizer and GSK, which have been paid to his employer. M.J.A. has conducted an unrelated consultancy for and received assistance with conference attendance from Sanofi. He has also received a speaker's fee from GSK. J.I. has received grants from AstraZeneca, Amgen, National Breast Cancer Foundation and Dementia Australia. R.G., S.W. and B.B. have no competing interests to declare.

AUTHOR CONTRIBUTIONS

Rukshar Gobarani: Conceptualization; data curation; formal analysis; investigation; methodology. **Jenni Ilomaki:** Supervision; validation. **Stephen Wood:** Formal analysis; methodology. **Michael Abramson:** Supervision; validation. **Billie Bonevski:** Supervision; validation. **Johnson George:** Resources; supervision; validation.

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REFERENCES

- World Health Organization. Tobacco 2020. [Accessed on: 3/03/2021]. Available from: <https://www.who.int/news-room/fact-sheets/detail/tobacco>
- Australian Institute of Health and Welfare. Alcohol, tobacco & other drugs in Australia Canberra: AIHW; 2019 Available from: <https://www.aihw.gov.au/reports/alcohol/alcohol-tobacco-other-drugs-australia>
- Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: An overview and network meta-analysis. *Cochrane Database Syst Rev.* 2013;5:CD009329.
- Karadoğan D, Önal Ö, Şahin DS, Kanbay Y, Alp S, Şahin Ü. Treatment adherence and short-term outcomes of smoking cessation outpatient clinic patients. *Tob Induc Dis.* 2018;16:38.
- Suehs BT, Davis C, Galaznik A, Joshi AV, Zou KH, Patel NC. Association of out-of-Pocket Pharmacy Costs with adherence to Varenicline. *J Manag Care Spec Pharm.* 2014;20(6):592–600.
- Drovandi AD, Chen CC, Glass BD. Adverse effects cause Varenicline discontinuation: A meta-analysis. *Curr Drug Saf.* 2016;11(1):78–85.
- Catz SL, Jack LM, McClure JB, Javitz HS, Deprey M, Zbikowski SM, et al. Adherence to varenicline in the COMPASS smoking cessation intervention trial. *Nicotine Tob Res.* 2011;13(5):361–8.
- Shah D, Shah A, Tan X, Sambamoorthi U. Trends in utilization of smoking cessation agents before and after the passage of FDA boxed warning in the United States. *Drug Alcohol Depend.* 2017;177:187–93.
- Jarlenski M, Hyon Baik S, Zhang Y. Trends in use of medications for smoking cessation in Medicare, 2007–2012. *Am J Prev Med.* 2016;51(3):301–8.
- Kasza KA, Cummings KM, Carpenter MJ, Cornelius ME, Hyland AJ, Fong GT. Use of stop-smoking medications in the United States before and after the introduction of varenicline. *Addiction.* 2015;110(2):346–55.
- U.S. Food and Drug Administration. Public health advisory: important information on Chantix (varenicline) 2008. [Accessed on: 22/12/2019] Available from: <http://wayback.archive-it.org/7993/20170112032505/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051136.htm>
- Davies NM, Thomas KH. The Food and Drug Administration and varenicline: Should risk communication be improved? *Addiction.* 2017;112(4):555–8.
- U.S. Food and Drug Administration. FDA Drug Safety Communication: Chantix (varenicline) may increase the risk of certain cardiovascular adverse events in patients with cardiovascular disease 2011. [Accessed on: 01 January 2020] Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-chantix-varenicline-may-increase-risk-certain-cardiovascular-adverse#data>
- Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. 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. *Lancet.* 2016;387(10037):2507–20.
- Thomas KH, Martin RM, Knipe DW, Higgins JP, Gunnell D. Risk of neuropsychiatric adverse events associated with varenicline: Systematic review and meta-analysis. *BMJ.* 2015;350:h1109.
- Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, et al. Cardiovascular safety of Varenicline, bupropion, and nicotine patch in smokers: A randomized clinical trial. *JAMA Intern Med.* 2018;178(5):622–31.
- Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: A randomized controlled trial. *Jama.* 2006;296(1):64–71.
- Livingstone-Banks J, Norris E, Hartmann-Boyce J, West R, Jarvis M, Chubb E, et al. Relapse prevention interventions for smoking cessation. *Cochrane Database Syst Rev.* 2019;10:CD003999.
- Schnoll R, Leone F, Veluz-Wilkins A, Miele A, Hole A, Jao NC, et al. A randomized controlled trial of 24 weeks of varenicline for tobacco use among cancer patients: Efficacy, safety, and adherence. *Psychooncology.* 2019;28(3):561–9.
- Australian Government Department of Health. Schedule of Pharmaceutical Benefits General Pharmaceutical Schedule - Volume 1. 2021. Available from: <https://www.pbs.gov.au>
- Pharmaceutical Benefits Advisory Committee. Post-market review of medicines for smoking cessation. 2021. Available from: <https://www.pbs.gov.au/reviews/post-market-smoking-cessation-files/draft-smoking-cessation-report-tor2.pdf>
- Paige E, Kemp-Casey A, Korda R, Banks E. Using Australian pharmaceutical benefits scheme data for pharmacoepidemiological research: Challenges and approaches. *Public Health Res Pract.* 2015;25(4):e2541546.
- Mellish L, Karanges EA, Litchfield MJ, Schaffer AL, Blanch B, Daniels BJ, et al. The Australian pharmaceutical benefits scheme data collection: A practical guide for researchers. *BMC Res Notes.* 2015;8(1):634.
- Pratt NL, Kerr M, Barratt JD, Kemp-Casey A, Kalisch Ellett LM, Ramsay E, et al. The validity of the Rx-risk comorbidity index using medicines mapped to the anatomical therapeutic chemical (ATC) classification system. *BMJ Open.* 2018;8(4):1–8.
- Hosmer Jr DW, Lemeshow S, Sturdivant RX. *Applied logistic regression: John Wiley & Sons;* 2013.
- Watkins SL, Thurl J, Max W, Ling PM. Real-world effectiveness of smoking cessation strategies for young and older adults: Findings from a nationally representative cohort. *Nicotine Tob Res.* 2020;22(9):1560–8.
- Clark MA, Rakowski W, Kviz FJ, Hogan JW. Age and stage of readiness for smoking cessation. *J Gerontol B Psychol Sci Soc Sci.* 1997;52B(4):S212–21.
- Huang Y, Lewis S, Britton J. Use of varenicline for smoking cessation treatment in UK primary care: An association rule mining analysis. *BMC Public Health.* 2014;14(1):1024.
- Desai RJ, Good MM, San-Juan-Rodriguez A, Henriksen A, Cunningham F, Hernandez I, et al. Varenicline and Nicotine Replacement Use Associated With US Food and Drug Administration Drug Safety Communications. *JAMA.* 2019;2(9):e1910626-e.
- Evins AE, Benowitz NL, West R, Russ C, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of Varenicline, bupropion, and nicotine patch in smokers with psychotic, anxiety, and mood disorders in the EAGLES trial. *J Clin Psychopharmacol.* 2019;39(2):108–16.
- Wetter DW, Kenford SL, Smith SS, Fiore MC, Jorenby DE, Baker TB. Gender differences in smoking cessation. *J Consult Clin Psychol.* 1999;67(4):555–62.
- Smith PH, Kasza KA, Hyland A, Fong GT, Borland R, Brady K, et al. Gender differences in medication use and cigarette smoking cessation: Results from the international tobacco control four country survey. *Nicotine Tob Res.* 2015;17(4):463–72.

33. Perkins KA, Scott J. Sex differences in long-term smoking cessation rates due to nicotine patch. *Nicotine Tob Res.* 2008;10(7):1245–50.
34. Scharf D, Shiffman S. Are there gender differences in smoking cessation, with and without bupropion? Pooled- and meta-analyses of clinical trials of bupropion SR. *Addiction.* 2004;99(11):1462–9.
35. McKee SA, Smith PH, Kaufman M, Mazure CM, Weinberger AH. Sex differences in Varenicline efficacy for smoking cessation: A meta-analysis. *Nicotine Tob Res.* 2016;18(5):1002–11.
36. Pharmaceutical Benefits Scheme. Post-market review of medicines used for smoking cessation: Report to PBAC: Background.; 2021. Available from: <https://www.pbs.gov.au/info/reviews/public-consultation-on-the-post-market-review-of-medicines>
37. Hynd A, Roughhead EE, Preen DB, Glover J, Bulsara M, Semmens J. The impact of co-payment increases on dispensings of government-subsidised medicines in Australia. *Pharmacoepidemiol Drug Saf.* 2008;17(11):1091–9.
38. Balmford J, Borland R, Hammond D, Cummings KM. Adherence to and reasons for premature discontinuation from stop-smoking medications: Data from the ITC four-country survey. *Nicotine Tob Res.* 2011;13(2):94–102.
39. Centers for Disease Control and Prevention. Tobacco use and quitting among individuals with behavioral health conditions updated 4 February 2020. [Accessed on: 29 October 2020] Available from: <https://www.cdc.gov/tobacco/disparities/mental-illness-substance-use/index.htm>
40. Gobarani RK, Abramson MJ, Bonevski B, Weeks GR, Dooley MJ, Smith BJ, et al. The efficacy and safety of varenicline alone versus in combination with nicotine lozenges for smoking cessation among hospitalised smokers (VANISH): Study protocol for a randomised, placebo-controlled trial. *BMJ Open.* 2020;10(10):e038184.
41. Koegelenberg CF, Noor F, Bateman ED, van Zyl-Smit RN, Bruning A, O'Brien JA, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: A randomized clinical trial. *Jama.* 2014;312(2):155–61.
42. Seal F, Cave JA, Atkinson LL. Primary non-adherence of prescribed pharmaceutical treatments and interventions: An investigative review to improve quality in primary care. *Qual Prim Care.* 2017; 25(5):344–59.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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