Effectiveness and safety of medicines used in COPD patients

Wang, Yuanyuan

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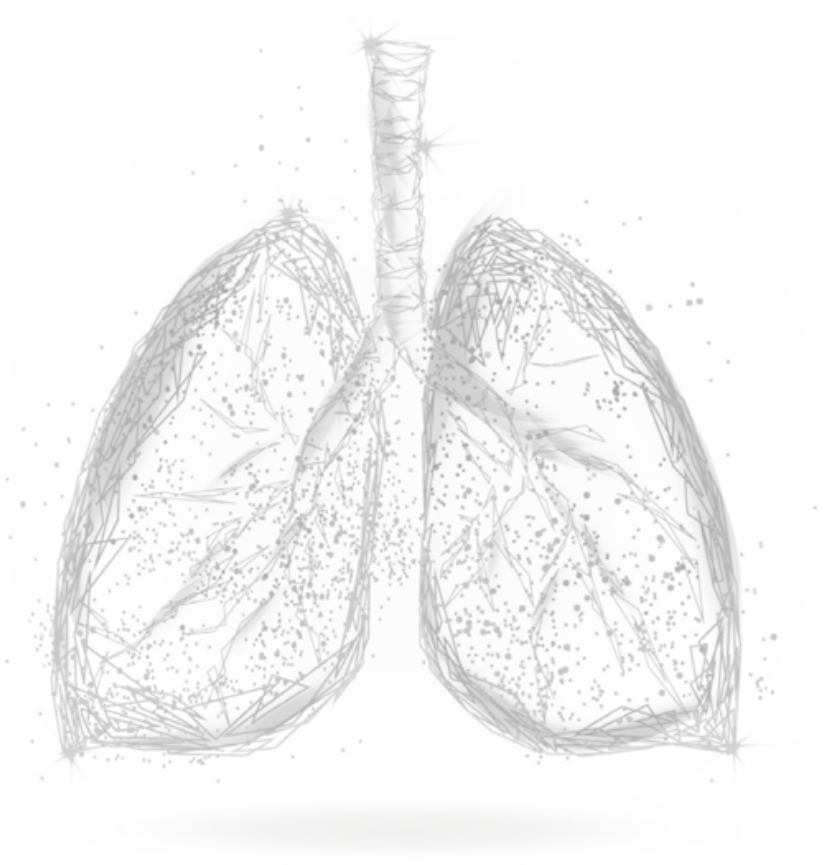
CHAPTER 7



Risk of neuropsychiatric adverse events associated with varenicline treatment for smoking cessation: a prescription sequence symmetry analysis

Yuanyuan Wang
Job F.M. van Boven
Jens H. Bos
Catharina C.M. Schuiling-Veninga
H. Marike Boezen
Bob Wilffert
Eelko Hak

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ABSTRACT

Background

Varenicline is an effective treatment for smoking cessation. While clinical trials among selected patients did not confirm a causal role, spontaneous reports from daily practice have suggested a possible risk of neuropsychiatric adverse events (NPAEs) by varenicline.

Objectives

To investigate the risk of NPAEs associated with varenicline initiation among the general population in a real-world setting.

Methods

We conducted a prescription sequence symmetry analysis (PSSA) using data from 2007 to 2018 from the University of Groningen IADB.nl prescription database. We selected incident users of both varenicline and marker drugs for NPAEs, including depression, anxiety and sleep disorder within different time-intervals (30, 60, 90, 180, 365 days). Adjusted sequence ratios (aSR) were calculated for each time-interval.

Results

Within 365-days' time-interval 1,066 patients were incident users of both varenicline and NPAE marker drugs. In total, 505 patients were prescribed varenicline before NPAE marker drugs and 561 vice versa (crude sequence ratio (cSR) 0.90, 95% CI: 0.80-1.02). After adjustments for trends in prescriptions, overall a null association was found (aSR 1.00, 95% CI: 0.89-1.13). Regarding specific NPAEs, no increased risks were found for depression nor anxiety within any time-interval. A small transient increased risk was found for sleep disorders, particularly in earlier time-intervals 3 months and 6 months (aSRs 1.52, [1.10, 2.11] and 1.45, [1.15, 1.83], respectively). The results were robust in stratified analyses by age and gender, and several sensitivity analyses.

Conclusions

Findings from this real-world study were generally consistent with the evidence from clinical trials. Varenicline initiation was not associated with an increased risk of taking anti-depressants nor anti-anxiety drugs, yet a small, but statistically significant, transient association with drugs for sleep disorders was noticed, possibly associated with withdrawal symptoms caused by smoking cessation.

INTRODUCTION

Although in many countries the prevalence of tobacco use has been declining in recent years,[1] the tobacco epidemic is still one of the largest global public health threats, related to more than 8 million deaths worldwide each year.[2] Smoking-related health problems, including cardiovascular and respiratory disease, are associated with a high burden for both family and society.[3] To help halt this burden, several pharmacological and non-pharmacological treatments are available. Varenicline, a first-line pharmacological smoking cessation treatment (PSCT), which was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2006. It has a unique mechanism of action compared with other PSCTs by acting as a partial agonist/antagonist with affinity and selectivity for $\alpha_4\beta_2$ nicotinic acetylcholine receptors.[4] In several randomized clinical trials (RCTs), varenicline was more effective for smoking cessation than bupropion, nicotine replacement therapy (NRT) or placebo.[5-7]

However, subsequent post-marketing reports related to neuropsychiatric adverse events (NPAEs), such as depression, anxiety, sleep disorder but also suicide, among varenicline users raised concerns about the neuropsychiatric safety of varenicline.[8] Based on the post-marketing surveillance reports, the FDA placed a black box warning on varenicline about its risk of NPAEs in 2009.[9] The spontaneous case-reports and the FDA warning may have confused both smokers and physicians regarding the causal role of varenicline in inducing NPAEs.[10] Such misunderstanding undoubtedly has led to the underutilization of varenicline for smoking cessation.[11-13]

Although case reports are important signals of drug safety, causality could not be established without using an adequate control group.[14] Therefore, to identify the causal association between varenicline and risk of NPAEs, several large cohort studies were conducted after the safety warning[15-19] as well as RCTs.[7,20,21] Notably, the synthesized evidence did not confirm the earlier suggestions from case reports about severe neuropsychiatric risk from varenicline use.[22-24] Therefore, the warning about possible suicidal risk from varenicline was removed by FDA in 2016. In subsequent years, doubts remained regarding the decision to lift the FDA warning. In particular, considering the relatively healthy population and limited power to detect rare events in clinical trials, results from RCTs may not reflect the situation in the real-world setting. Moreover, evidence from available observational cohort studies is inconsistent, and these studies were criticized for their potential bias (e.g. selection bias) and confounding (e.g. residual confounding).[25]

To overcome this bias, the prescription sequence symmetry analysis (PSSA) has been proposed to investigate acute adverse effects of medications, with moderate sensitivity, high specificity and robust performance.[26-28] Unlike spontaneous reporting systems, it uses individual prescription or hospitalization data to assess the association between

a medication and an adverse drug reaction (ADR) by examining the symmetry in the sequence of index medication and marker medications as proxy for ADRs within a specific time window.[27,29] Compared with traditional observational studies (i.e. cohort or case-control), PSSA controls genetic and other time-invariant confounding effectively due to its self-controlled study design. Of note, the relationship between varenicline and NPAEs has not been studied before by using PSSA.

The aim of this study was to examine whether there is an association between varenicline use and onset of NPAEs in the real-world setting using PSSA.

METHODS

Data source and setting

This study was conducted using the widely researched University of Groningen's pharmacy prescription database IADB.nl, a growing database that comprises a population of approximately 730,000 people from 72 community pharmacies in the northern Netherlands since 1994, regardless of type of health insurance.[30] The individuals are representative of the Dutch population with respect to drug use. Detailed prescription information includes date of prescription, name of dispensed drug, dosage, duration and related Anatomical Therapeutic Chemical (ATC) code of prescribed drug, but also year of birth and gender. As Dutch patients usually register at one single community pharmacy, the prescription information from pharmacies are relatively complete. Of note, over-the-counter drugs and prescriptions during hospital stay are not included in IADB.nl. Data after registration of varenicline from 2007 to 2018 were used for this study. The IADB.nl has been used in several previous PSSAs.[31,32]

Study design

The applied PSSA design compares the frequency of initiation of a marker drug (as proxy for an ADR) before and after initiation of an index drug within the same individual. The individuals who were prescribed the index drug (i.e. varenicline) before marker drugs for NPAEs were labeled the "causal group". Conversely, those who were prescribed varenicline after the marker drugs were labeled the "non-causal group". The crude sequence ratio (cSR) was defined by the number of patients in the causal group divided by the number of patients in the non-causal group which reflects the association between exposure and outcome. If there is no association, the distribution of sequence orders is expected to be symmetrical and the SR is close to 1. Of note, the PSSA design is sensitive to changing trends in drug prescriptions over time, which could be caused by factors like reimbursement policy changes and safety warnings. Therefore, a null-effect sequence ratio (nSR) was used to adjust for the temporal prescription trends of varenicline and marker drugs for ADRs.[29] This trend can be used to estimate the probability of varenicline

to be prescribed first, in the absence of any causal relationship. The adjusted sequence ratio (aSR) was calculated by dividing the cSR by the nSR.

Run-in period

As the goal of PSSA is to evaluate the relation between two incident events, we needed to identify the incident users of both index and marker drugs. As our index drug, i.e. varenicline, was authorized for use by EMA on 26 September 2006, no varenicline was prescribed in the database IADB.nl before 2007. Therefore, in theory, patients with the first recorded prescription of varenicline during the study period were all incident users. Since the marker drugs have long been used for chronic treatment of NPAEs, most of their current users will be captured at the beginning of the study period. To exclude the current users and identify incident users of NPAEs marker drugs, we used the waiting time distribution to determine the run-in period.[33]

Study population and time interval

This study included all individuals who were incident users of both varenicline (ATC: N07BA03) and any marker drugs as potential treatment for NPAEs including depression (N06B, N06CA), anxiety (N05B) and sleep disorder (N05C) from 1 January 2007 to 31 December 2018 in IADB.nl. The first prescription of varenicline was the index date of varenicline, the first prescription of any of the marker drugs for NPAEs was set as index date of any NPAEs. The first prescription of specific marker drugs for depression, anxiety and sleep disorder were set as index date of specific NPAE. Those who were prescribed the index and marker drug on the same day were excluded.

We defined different time-intervals (365 days, 180 days, 90 days, 60 days and 30 days) between the initiation of the varenicline and NPAEs marker drugs to explore their association. Therefore, incident users of both varenicline and marker drugs, irrespective of dose and duration, within pre-set time intervals of each other were included for the PSSA.

Statistical analysis

The crude sequence ratio (cSR) was calculated by dividing the number of individuals in the causal group with the number of individuals in the non-causal group. The adjusted SR (aSR) was calculated by adjusting the time trend of the crude SR. A null-effect SR (nSR) is the expected SR without any causal associations. Therefore, the aSR is calculated as the ratio of crude SR to null-effect SR (cSR/nSR). The detailed formula were as follows:

(1) cSR = number of patients in the causal group/number of patients in the non-causal group.

(2) $$\text{nSR}= P_\alpha/1\text{-}P_\alpha,\ P_\alpha = \frac{\sum_{m=1}^{u}[A_m(\sum_{n=m+1}^{m+d} B_n)]}{\sum_{m=1}^{u}[A_m(\sum_{n=m-d}^{m-1} B_n+\sum_{n=m+1}^{m+d} B_n)]}$$

In the above formula, u is the last day of the research period, m and n are the consecutive days of the survey period, d is the time interval between index and marker drugs. A_m is the number of individuals being prescribed the index drug first on the m day. B_n is the number of individuals being prescribed marker drugs first on the n day.

(3) $$aSR = cSR/nSR$$

Confidence intervals (95% CI) of cSR and aSR were calculated by using the binomial distribution as follows:

$$95\%\ CI = e^{In(SR)\pm 1.96SE},$$

where standard error

$$(SE) = \sqrt{\frac{1}{number\ of\ causal\ group} + \frac{1}{number\ of\ non-causual\ group}}$$

All statistical analyses were performed using IBM SPSS statistics 25 (IBM Corporation, Armonk, NY, USA) for Windows. We defined $p<0.05$ as the level of statistical significance. All statistical tests were two tailed.

Subgroup and sensitivity analyses

Stratified analysis was conducted according to different gender and age groups. We considered that several policy changes occurred during the study period: (1) reimbursement of PSCTs: PSCTs were reimbursed in 2011, non-reimbursed in 2012 and again reimbursed from 2013 onwards. (2) Black box warning: FDA communicated it in 2009 and removed it in 2016; we performed sensitivity analyses by calculating the aSR for each year of the study period, as well as in several year groups.

RESULTS

Study population

In total, there were 6,440 patients who initiated both varenicline and marker drugs for NPAEs between 2007 to 2018 (Figure 1). Of these, 17 patients were excluded because they were prescribed varenicline and marker drugs at the same day. Of the remaining 4,966 patients, 1,457 were excluded because they were in the run-in period of three months. As shown in the waiting-time distribution (Figure 2), there was a steep decrease at the beginning of the study period after which a more or less stable situation was reached after 3 months, i.e. when prevalent users were basically not in the newly captured population. Finally, for our PSSA there were 1,066 patients who were incident users of both varenicline and marker drugs that were prescribed within a 1-year time

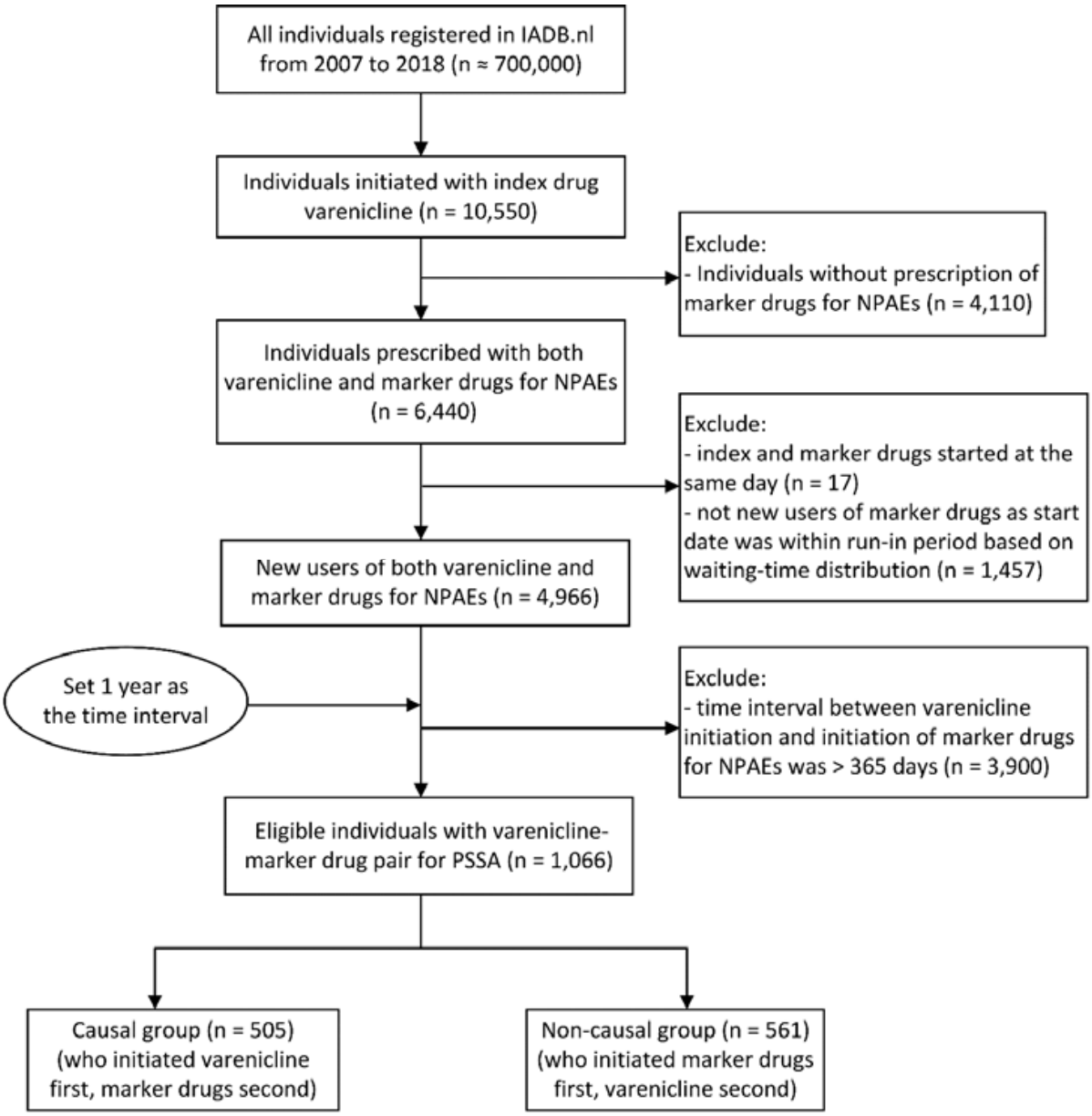

Figure 1. Flow chart of study population selection.

period of each other. General characteristics on the study population are shown in Table 1. The median age was 47 years (IQR 18) and the median number of medications that were prescribed before enrollment was 1 (IQR 3). There were no statistically significant differences in age, gender, number of medications prescribed one year before enrollment and distribution of specific diseases identified by related medications between causal and non-causal groups.

Main outcome

In total, there were 505 patients in the causal group and 561 patients in the non-causal group. Over the full 365 days study follow-up, no statistically significant difference was observed between the two groups. The aSR between varenicline and any NPAEs was

Table 1. Characteristics of the study population in the prescription sequence symmetry analysis.

Characteristics	Total population (N = 1066)	Causal group[a] (n = 505)	Non-casual group[b] (n = 561)	P-value[*]
Gender (n, %)				0.677
Male	529 (49.6)	254 (50.3)	275 (49.0)	
Female	537 (50.4)	251 (49.7)	286 (51.0)	
Age groups (n, %)				
Median (IQR)	47 (18)	48 (19)	47 (17)	
<= 40	323 (30.3)	152 (30.1)	171 (30.5)	0.299
40 - 50	307 (28.8)	135 (26.7)	172 (30.7)	
50 - 60	290 (27.2)	150 (29.7)	140 (25.0)	
> 60	146 (13.7)	68 (13.5)	78 (13.9)	
Number of total medications 1 year before enrolment[#] (n, %)				
Median (IQR)	1 (3)	1 (3)	1 (3)	
0	406 (38.1)	189 (37.4)	217 (38.7)	0.924
1	197 (18.5)	95 (18.8)	102 (18.2)	
2-3	249 (23.4)	116 (23.0)	133 (23.7)	
>= 4	214 (20.1)	105 (20.8)	109 (19.4)	
Number of patients with specific medication use (n, %)				
For obstructive airway diseases (ATC codes: R03)	198 (18.6)	100 (19.8)	98 (17.5)	0.328
For cardiac diseases (C01)	27 (2.5)	16 (3.2)	11 (2.0)	0.210
For diabetes (A10)	52 (4.9)	27 (5.3)	25 (4.5)	0.500

Note: ATC: The Anatomical Therapeutic Chemical (ATC);

[a]Causal group: patients prescribed varenicline first following by marker drugs for NPAEs.

[b]Non-causal group: patients prescribed marker drugs for NPAEs first, following by varenicline.

[*]Chi-square test; [#]Enrollment: the original prescribing date of varenicline of patients in causal group or the original prescribing date of marker drugs for NPAEs of patients in non-causal group.

1.00 [95% CI: 0.89, 1.13, Table 2]. Also, no statistical significant association was observed between varenicline and the occurrence of depression (aSR 1.09 [95% CI: 0.94, 1.26]) nor anxiety (aSR 0.98 [0.85, 1.14]). There was, however, a small statistically significant increased risk of sleep disorders observed associated with varenicline (aSR 1.25 [95% CI: 1.05, 1.48]).

Impact of time intervals

When we considered different time-intervals between initiation of varenicline and any NPAE marker drugs, we also did not find significant associations (Table 2) within 30 days (aSR 0.96, [0.66, 1.39]) and 60 days (aSR 1.10, [0.84, 1.44]. However, there was a boundary significant increased risk of NPAEs observed with varenicline within 90 and 180 days.

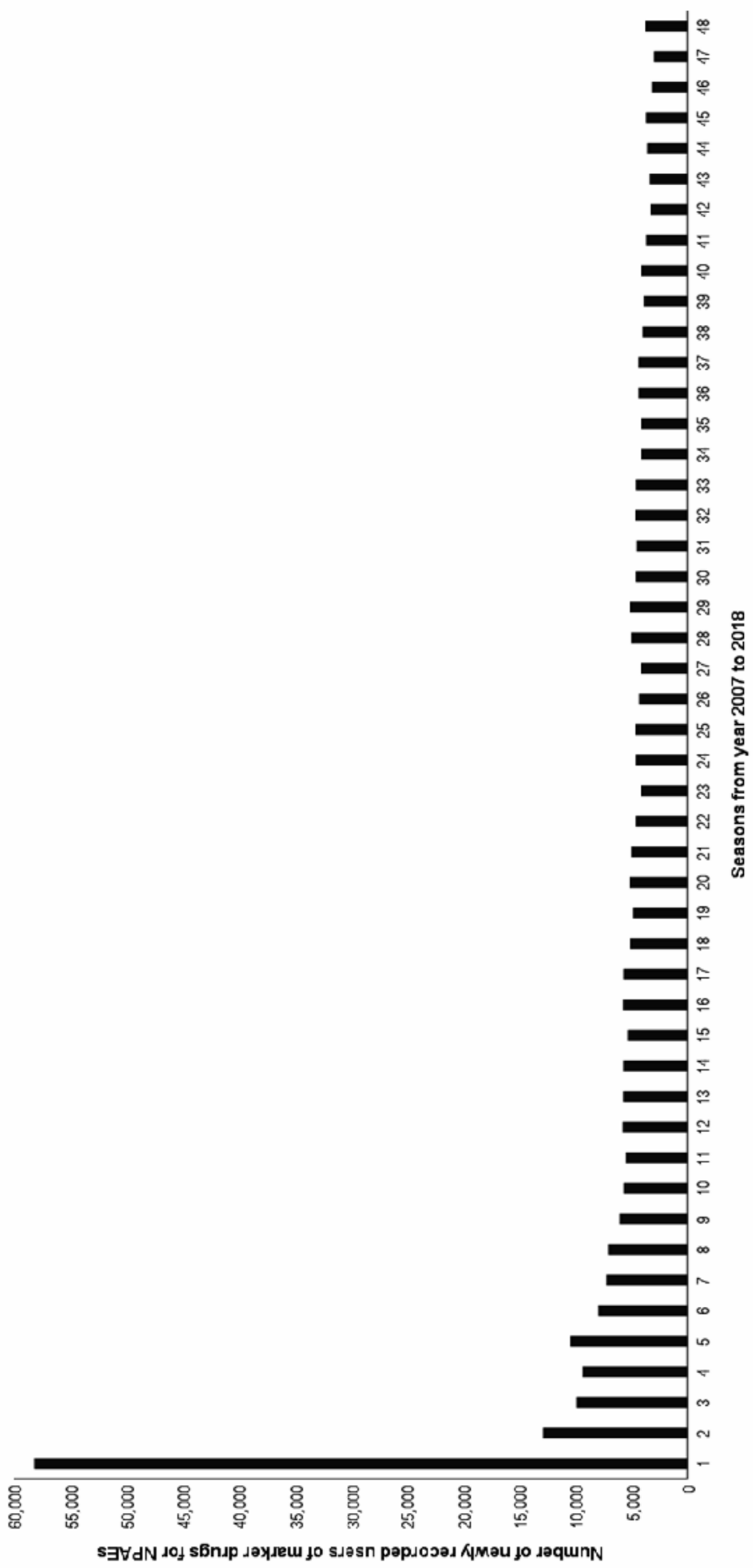

Figure 2. Waiting time distribution of the first prescriptions of marker drugs for NPAEs with the 1st year of study period.

Table 2. Results of the prescription sequence symmetry analysis for the association between varenicline use and marker drugs use for NPAEs by different time periods.

NPAEs	Population* (n)	Causal group (n)	Non-causal group (n)	cSR (95% CI)	nSR	aSR (95% CI)
Within 365 days						
Overall	1066	505	561	0.90 [0.80, 1.02]	0.900	1.00 [0.89, 1.13]
depression	727	364	363	1.00 [0.87, 1.16]	0.924	1.09 [0.94, 1.26]
anxiety	716	335	381	0.88 [0.76, 1.02]	0.893	0.98 [0.85, 1.14]
sleepdisorder	532	286	246	1.16 [0.98, 1.38]	0.931	1.25 [1.05, 1.48]
Within 180 days						
Overall	603	322	281	1.15 [0.98, 1.34]	0.949	1.21 [1.03, 1.42]
depression	389	208	181	1.15 [0.94, 1.40]	0.964	1.19 [0.98, 1.45]
anxiety	394	206	188	1.10 [0.90, 1.34]	0.943	1.16 [0.95, 1.42]
sleepdisorder	295	172	123	1.40 [1.11, 1.76]	0.965	1.45 [1.15, 1.83]
Within 90 days						
Overall	315	173	142	1.22 [0.98,1.52]	0.975	1.25 [1.00, 1.56]
depression	209	110	99	1.11 [0.85, 1.46]	0.984	1.13 [0.86, 1.48]
anxiety	189	99	90	1.10 [0.83, 1.46]	0.971	1.13 [0.85, 1.51]
sleepdisorder	150	90	60	1.50 [1.08, 2.08]	0.984	1.52 [1.10, 2.11]
Within 60 days						
Overall	212	110	102	1.08 [0.82, 1.41]	0.982	1.10 [0.84, 1.44]
depression	138	62	76	0.82 [0.58, 1.14]	0.989	0.83 [0.59, 1.15]
anxiety	137	72	65	1.11 [0.79, 1.55]	0.979	1.13 [0.81, 1.58]
sleepdisorder	101	56	45	1.24 [0.84, 1.84]	0.990	1.26 [0.85, 1.86]
Within 30 days						
Overall	111	54	57	0.95 [0.65,1.37]	0.988	0.96 [0.66, 1.39]
depression	74	31	43	0.72 [0.45, 1.14]	0.993	0.73 [0.46, 1.15]
anxiety	73	32	41	0.76 [0.47, 1.21]	0.986	0.77 [0.48, 1.22]
sleep disorder	50	25	25	1.00 [0.57, 1.74]	0.993	1.01 [0.58, 1.77]

NPAEs: neuropsychiatric adverse events. cSR: crude sequence ratio; aSR: adjusted sequence ratio; nSR: null-effect sequence ratio; CI: confidence interval;

For the specific NPAEs, similar to the results observed within 365 days, no significant associations were observed between varenicline and specific NPAEs. Again, sleep disorder was the exception with an aSR of 1.52 [95% CI: 1.10, 2.11] and 1.45 [95% CI: 1.15, 1.83] within 90 and 180 days, respectively. Frequency distributions of patients with any NPAE or specific NPAE (depression, anxiety and sleep disorder) are shown in Figure 3.

Subgroup and sensitivity analyses

In stratified analyses by gender and age groups (Table S1), a significant association between varenicline and sleep disorder was only seen in female and older age groups. Of note, a boundary significant risk of depression associated with varenicline was also

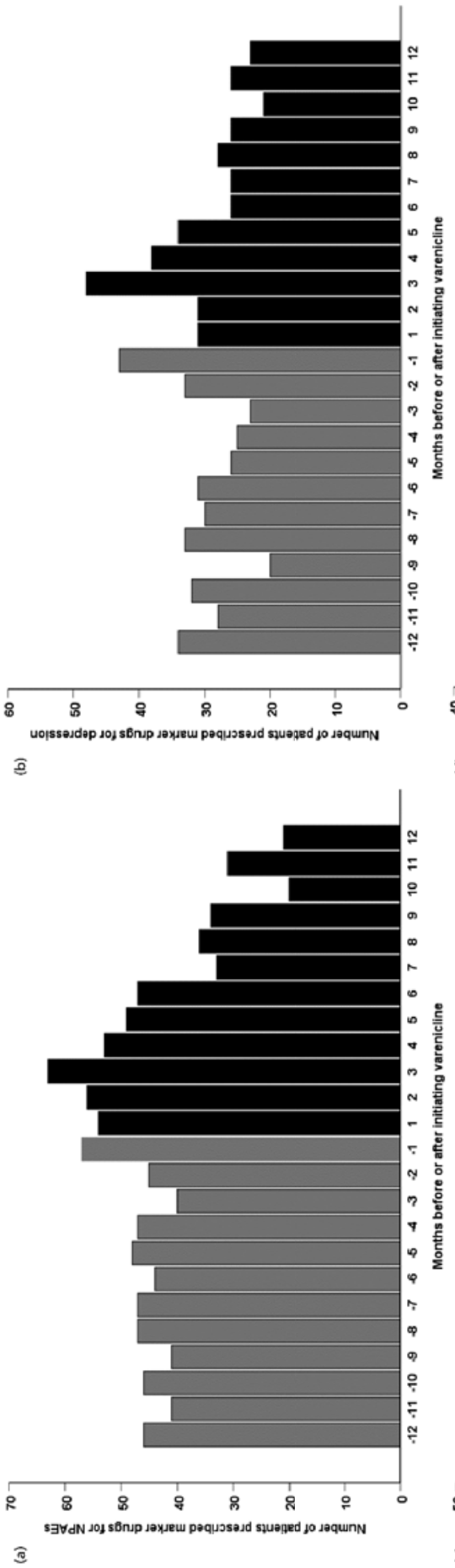

Figure 3. Frequency distribution of patients with (a) all NPAEs; (b) depression; (c) anxiety; (d) sleep disorder by number of months before or after the initiation of varenicline within 1 year.

observed in older age groups (aSR 1.23, 95% CI: 1.01-1.50]). As shown in Figure S1, there were three main fluctuations in the curve for the number of patients newly prescribed varenicline by years of study period. There was a high rise in newly prescribed varenicline in 2011 and a drop in 2012, followed by a sharp increase in 2013. Also, there was a small increase in newly prescribed varenicline from 2015 to 2016. In the results of sensitivity analysis by year groups or each year for the aSR between varenicline and overall NPAEs, we did not observe any statistical significant difference for the order of causal and non-causal-groups, except for year 2011 (aSR 1.72, 95% CI: 1.27, 2.32, Table S2).

DISCUSSION

Main findings

This is the first study to assess the risk of NPAEs associated with varenicline by applying a PSSA design. Based on the results of this study, we further confirm that no statistical significant increased risk of anti-anxiety and anti-depressant drug prescription was associated with varenicline prescription in all different time-intervals. However, within 3, 6 and 12 months, there was a small, but statistically significant, increased risk of sleep disorder. We did not observe significant risk of sleep disorder associated with varenicline within shorter time-intervals (1 or 2 months).

Interpretation

The results of this study are consistent with a large meta-analysis of RCTs published in 2015,[22] regarding mood change and sleeping disorders. In this systematic review involving 39 studies, there was no evidence of an increased risk of depression and anxiety among varenicline users, compared with placebo users. Oppositely, a higher risk of sleep problems (e.g. insomnia, abnormal dreams) was observed, which was also seen in our study. Of note, different from PSSA as a self-controlled design, most previous observational cohort studies used nicotine replacement therapy (NRTs) as the reference group to explore the risk of NPAEs associated with varenicline. In two large cohort studies, there was also no increased depression risk observed among varenicline users.[15,16] However, in a third cohort study, varenicline was found to be associated with a small increase in the risk of anxiety and mood conditions, but this was only observed in people with previous psychiatric disorders.[17]

Sleep disorder is well recognized as a commonly reported ADR associated with varenicline in clinical trials with an incidence ranging from 14.0% to 37.2%.[4] It was also the most frequently reported psychiatric event (1.6%) according to a prescription-event monitoring study based in general practice in England.[8] However, it is difficult to identify whether sleeping problems are due to side effects of PSCTs or related to withdrawal from nicotine. Indeed, difficulty falling asleep and increased number of awakenings are also common symptoms of nicotine withdrawal.[34] Although sleep disorder is not

a serious ADR, it may result in poor adherence to varenicline and therefore potentially affect the possibility of quitting successfully. As such, clinicians should pay particular attention to this kind of side effect among varenicline users.

Of note, there was a traditional self-controlled analysis conducted by Gershon et al. in 2018,[35] that compared the relative incidence of hospitalizations and emergency department visits during the period of varenicline use compared to the period without varenicline use. The relative incidence (RI) of NPAEs was significantly increased (RI 1.06; 95%CI: 1.00-1.13). Considering that the boundary significant result was not robust in sensitivity analyses and subgroup analyses stratified by age groups, the authors did not come to a firm conclusion about the risk of NPAEs associated with varenicline. Compared with this previous study that focused on inpatients, we focused more on NPAEs that happened among outpatients by using a different self-controlled study design (i.e. PSSA). Combining the results from our study and the study by Gershon et al, provides complimentary varenicline safety evidence for the general population among different real-world settings.

Considering PSSA is sensitive to fluctuation of medication prescriptions, we did sensitivity analyses by calculating the aSR in each year of the study period. We observed fairly consistent results except for the year 2011, which may be biased by PSCT reimbursement policy changes in the Netherlands since PSCTs were reimbursed in 2011 and the reimbursement was temporarily discontinued in 2012.[36] Before the cancellation of reimbursement, more varenicline was prescribed in 2011, the sharp increase of varenicline may have led to more people falling in the causal group (varenicline first and maker drugs second) and less people falling into the non-causal group, which might have led to the aSR above 1. It's reported that females and older people are more sensitive to NPAEs.[37-39] However, we did not find a significant risk of any NPAEs associated with varenicline in these sub-groups except for sleep disorders, which is consistent with our original outcomes and showed the robustness of our results.

Strengths and limitations

Our study has several strengths. The major strength of PSSA design is that it inherently controls for time-invariant, patient-specific confounders (e.g., sociodemographic characteristics, genetic and lifestyle-related factors) compared with other observational study designs such as cohort or case-control.[26] Second, we used a large prescription database with information about medicines dispensed in community pharmacies in the Netherlands, which is representative for a general, unselected, population. Third, due to our design we went beyond the question whether varenicline-related ADRs occurred, and could also provide in-depth analysis of their timing. Our study also has several potential limitations. First, PSSA is sensitive to time-varying confounding like disease severity, which could possibly affect the prescription of sequence of the index

and marker drugs. To minimize this time-varying bias, we limited the time window between index and marker drugs to a maximum of 12 months. Furthermore, due to absence of diagnostic data, marker drugs were used as proxy for NPAEs. Lastly, some severe NPAEs like suicide, neuropsychiatric hospitalizations and emergency department visits could not be evaluated. Despite these limitations are inherent to PSSA methods and common in real-world data sources, this study provides good supplementary evidence for the risk of NPAEs associated with varenicline use in a real-word setting.

Recommendations for future research, policy and clinical practice

Our results re-assure the safety of varenicline and may help further minimizing the doubt regarding potential severe adverse drug reactions related to varenicline and support the removal of FDA's black box warning. Clinicians and users of varenicline should however remain aware of increased occurrence of sleep disorder, especially in the first three to six months after varenicline initiation. Proper education on expected timing of this event and personalized coping strategies is particularly required. Eventually, this may result in increased smoking cessation treatment uptake, adherence and, ultimately, cessation rates. Future research should focus on whether this sleep disorder is caused by varenicline itself or more related to withdrawal of nicotine.

CONCLUSIONS

Our PSSA results suggest that real-world use of varenicline is not associated with any serious risk of NPAEs. However, consistent with previous evidence, there was a transient increased risk of sleep disorder associated with varenicline initiation, particularly in the first three to six months. Whether sleep disorder was caused by the adverse effects of varenicline or related to withdrawal symptoms needs further study.

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SUPPLEMENTARY MATERIALS

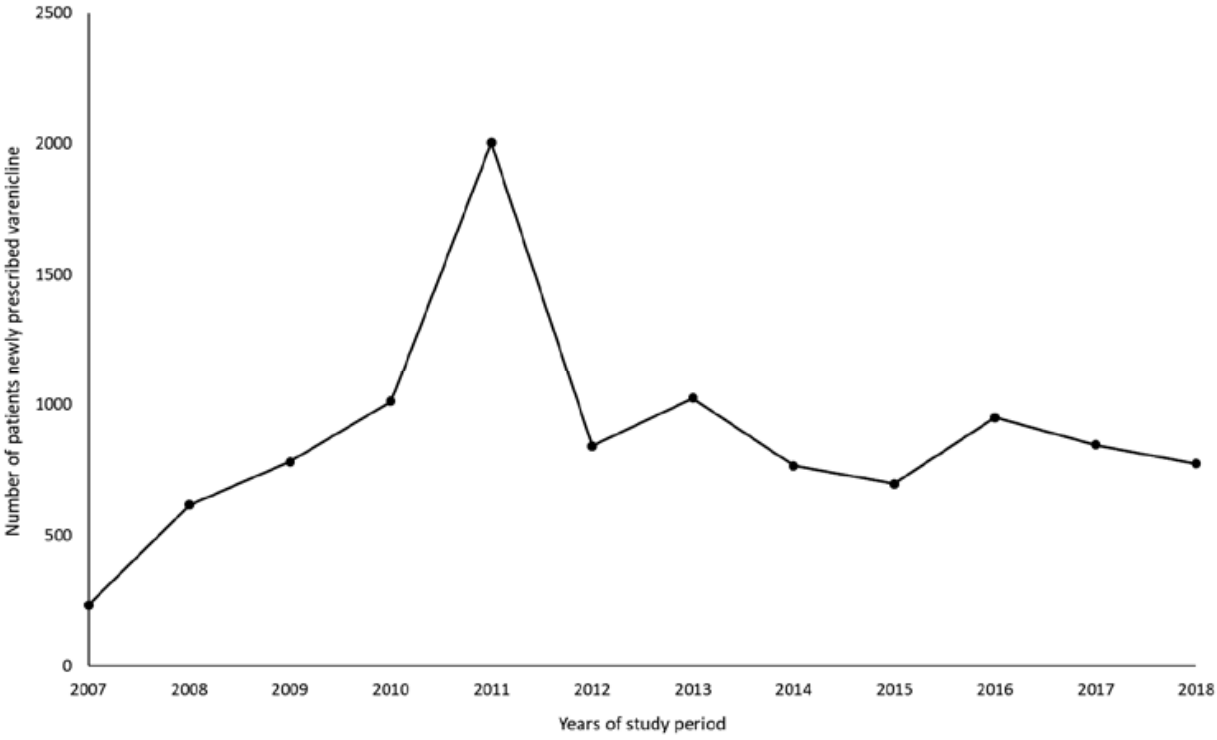

Figure S1. Number of patients newly prescribed varenicline in each year of the study period

Table S1. Prescription sequence symmetry results of the association between varenilcine use and marker drugs for NPAEs within a time window of 1 year, stratified by year.

Time periods	Number of patients*	Sequence order[a]	Crude SR	Null-effect SR	Adjusted SR
Year groups					
2007-2010	430	164/266	0.62 [0.51, 0.75]	0.75	0.82 [0.67, 1.00]
2011-2013	345	199/146	1.36 [1.10, 1.69]	1.10	1.23 [1.00, 1.53]
2014-2018	291	142/149	0.95 [0.76, 1.20]	0.96	0.99 [0.79, 1.25]
Year					
2007	75	19/56	0.34 [0.20, 0.57]	0.62	0.55 [0.33, 0.93]
2008	122	41/81	0.51 [0.35, 0.74]	0.70	0.72 [0.49, 1.05]
2009	103	42/61	0.69 [0.46, 1.02]	0.97	0.71 [0.48, 1.06]
2010	130	62/68	0.91 [0.65, 1.29]	0.98	0.93 [0.66, 1.32]
2011	173	99/74	1.34 [0.99, 1.81]	0.78	1.72 [1.27, 2.32]#
2012	73	44/29	1.52 [0.95, 2.42]	1.06	1.43 [0.89, 2.28]
2013	99	56/43	1.30 [0.88, 1.94]	1.27	1.02 [0.69, 1.52]
2014	67	30/37	0.81 [0.50, 1.31]	0.98	0.83 [0.51, 1.34]
2015	58	25/33	0.76 [0.45, 1.27]	0.92	0.83 [0.49, 1.39]
2016	65	36/29	1.24 [0.76, 2.02]	0.83	1.50 [0.92, 2.44]
2017	69	35/34	1.03 [0.64, 1.65]	1.08	0.95 [0.59, 1.52]
2018	32	16/16	1.00 [0.50, 2.00]	1.11	0.90 [0.45, 1.80]

*Patients with initial prescription of both index drug varenicline and marker drugs for NPAEs. #p<0.05, with statistical significance.
[a] the number of patients who initiated marker drugs for NPAEs after index drug varenicline divided by the number of patients who initiated varenicline after marker drugs for NPAEs. NPAEs: neuropsychiatric adverse events; SR: sequence ratio;

Table S2. Prescription sequence symmetry results of the association between varenicline use and marker drugs for NPAEs within a time window of 365 days, stratified by gender and age groups.

Variables	Number of patients*	Sequence order[a]	Crude SR	Null-effect SR	Adjusted SR
Gender					
Male					
Any NPAEs	529	254/275	0.92 [0.78, 1.10]	0.91	1.02 [0.86,1.21]
Depression	307	149/158	0.94 [0.75, 1.18]	0.92	1.02 [0.82, 1.28]
Anxiety	333	151/182	0.83 [0.67, 1.03]	0.90	0.92 [0.74, 1.15]
Sleep disorder	254	136/118	1.15 [0.90, 1.47]	0.94	1.22 [0.95, 1.56]
Female					
Any NPAEs	537	251/286	0.88 [0.74, 1.04]	0.90	0.98 [0.83, 1.16]
Depression	420	215/205	1.05 [0.87, 1.27]	0.93	1.13 [0.94, 1.37]
Anxiety	383	184/199	0.92 [0.76, 1.13]	0.89	1.04 [0.85, 1.27]
Sleep disorder	278	150/128	1.17 [0.93, 1.48]	0.92	1.27 [1.00, 1.61]#
Age groups					
< = 45 years					
Any NPAEs	476	214/262	0.82 [0.68, 0.98]	0.91	0.89 [0.75, 1.07]
Depression	326	151/175	0.86 [0.69, 1.07]	0.93	0.93 [0.75, 1.15]
Anxiety	323	136/187	0.73 [0.58, 0.91]	0.90	0.81 [0.65, 1.01]
Sleep disorder	234	116/118	0.98 [0.76, 1.27]	0.95	1.04 [0.80, 1.34]
> 45 years					
Any NPAEs	590	291/299	0.97 [0.83, 1.14]	0.89	1.10 [0.93, 1.29]
Depression	401	213/188	1.13 [0.93, 1.38]	0.92	1.23 [1.01, 1.50]
Anxiety	393	199/194	1.03 [0.84, 1.25]	0.89	1.16 [0.95, 1.41]
Sleep disorder	298	170/128	1.33 [1.06, 1.67]	0.92	1.44 [1.15, 1.82]#

*Patients with initial prescription of both index drug varenicline and maker drugs for NPAEs. [a] the number of patients who initiated marker drugs for NPAEs after index drug varenicline divided by the number of patients who initiated varenicline after marker drugs for NPAEs. #P<0.05; NPAEs: neuropsychiatric adverse events; SR: sequence ratio;