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TITLE

Varenicline and the risk of psychiatric disorders, suicidal behaviour, criminal offending, and transport accidents and offences: population-based cohort study

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ABSTRACT

Objectives To examine associations between varenicline and incidence of a range of adverse outcomes.

Design Population-based cohort study using within-individual analyses in order to control for confounding by indication.

Setting Whole population of Sweden.

Participants Of 7 847 679 individuals aged 15 and over investigated, 69 757 were prescribed varenicline between 2006 and 2009. Information on varenicline medication was collected from the Prescribed Drug Register.

Main outcome measures Incidence of new psychiatric disorders, suicidal behaviour, suspected and convicted criminal offending, transport accidents, and suspected and convicted traffic offences. Outcome information was collected from the high quality national registers.

Results In the whole population, 337393 psychiatric events occurred during follow-up. Furthermore, 507823 suspected and 338608 convicted crime events, 40595 suicidal events, 124445 transport accident events, 99895 suspected and 57068 convicted traffic crime events occurred during follow-up. Within-individual analyses demonstrated that varenicline was not associated with significant hazards of suicidal behaviour, criminal offending, transport accidents, traffic offences, or psychoses. However, varenicline was associated with a small increased risk of anxiety disorders (hazard ratio 1.27, 95% confidence interval 1.06 to 1.51), and mood disorders (1.28, 1.07 to 1.52).

Conclusions Concerns that varenicline is associated with increased risk of many adverse outcomes, including suicidality and accidents, is not supported in this observational study. The small increased risk in two psychiatric disorders needs confirmation using other research designs.

INTRODUCTION

Around 1.3 billion people in the world smoke tobacco[1], and tobacco use is the second leading risk factor contributing to global disease burden,[2] accounting for 9% of deaths globally and 18% of deaths in high-income countries.[3] Smoking cessation therapies include nicotine replacement therapies (NRTs) and nicotine-free prescription drugs. Increasingly, tobacco dependence is treated with varenicline (marketed as Champix® or Chantix®). Varenicline acts as a nicotinic acetylcholine receptor partial agonist that simultaneously relieves withdrawal symptoms and decreases rewards from smoking. Multiple studies have shown that varenicline is more efficacious than placebo, bupropion, or single forms of NRT.[4] Between approval in 2006 by the Food and Drug Administration (FDA) and mid-2011, 8.9 million individuals were treated with varenicline in the US.[5] In the UK, varenicline was prescribed to over 800.000 patients in primary care in 2009 and is one of the most common smoking cessation drugs.[6]

After varenicline's introduction on the market, reports of suicidality and depression emerged in post-marketing surveillance, and eventually led to warnings issued by regulatory agencies in Europe, and a black-box warning in the US.[7 8] Furthermore, varenicline has been reported to increase the risk of traffic accidents,[9] and has been restricted or prohibited for several transportation industry professions, including pilots, air traffic controllers, truck and bus drivers, and certain military personnel.[9 10] There is also some weaker evidence for increased violence[10] and psychosis risk.[11-15] However, these increased risks are based on post-marketing surveillance and case reports, [9 11-19] and not consistent with observational data and randomised controlled trials (RCTs) that have found no association between varenicline and depression, suicidality, or violence.[4,20-28] These inconsistencies could be explained by differences in study designs, confounding by comorbid psychiatric disorders or by indication (i.e. the same factors may influence both instituting treatment and outcomes), or reporting bias.[29] Moreover, individuals with mental health problems make up a substantial proportion of smokers.[30] However, the safety of varenicline has not been established among individuals with pre-existing mental health problems as they have either been excluded or trials have been comprised of small samples,[31] resulting in limited statistical power to detect rare events.[32-35]

To address limitations of previous research, we used a within-individual design where an individual is measured repeatedly over time, and treatment and non-

treatment periods are compared within the same person. Using this approach, the individual serves as his or her own control, thus adjusting for all time-invariant confounders during follow-up (i.e. genetic factors, all factors up to the start of follow-up and that remain constant during follow-up). Through this design, selection effects can be minimised, unmeasured confounders can be adjusted for, and confounding by indication can be addressed. [29]

We report a within-individual design to examine the association between varenicline and incidence of new psychiatric disorders, suicidal behaviour, suspected and convicted crimes, transport accidents, and suspected and convicted traffic offences in a large population-based Swedish cohort followed from 2006 to 2009.

METHODS

In the total population of Sweden aged 15 and over (N=7 847 679), we identified 69 757 individuals who were prescribed varenicline between November 22, 2006 (i.e. the introduction of varenicline in Sweden) and December 31, 2009. Information on individuals was collected from Swedish population-based registers with national coverage, and registers were linked using each individual's unique identification number.

Measures

Varenicline treatment

The Prescribed Drug Register includes information on all prescribed and collected medical drugs since July 2005.[36] Varenicline treatment was defined as at least one collected prescription of a varenicline (N07BA03) prescription between November 22, 2006 and December 31, 2009. Varenicline is recommended to be taken as a 12-week treatment;[37] a treatment period was thus defined to start at the date of the first collected prescription, and end 12 weeks later. Because varenicline is often divided into several prescriptions for the same 12-week treatment, collected prescriptions within 12 weeks of the first collected prescription were considered to be part of the same treatment period. Prescription collections occurring more than 12 weeks after a prior collection were considered as a new treatment period, and starting at the date of the next collected prescription .

Outcomes

Crimes

Crimes were defined as all offences in the penal code, except traffic offences. Information on convicted crimes for individuals aged 15 and older (the age of criminal responsibility) was extracted from the National Crime Register, including all convictions in Swedish district courts.[38] Suspected crimes were extracted from the Register of Person Suspected of Offences and include all individuals suspected of crime after a completed investigation by police, the customs authority, or the prosecution service.[39]

Incidence of new psychiatric disorders

Information on incidence of new psychiatric disorders was collected from the Patient Register,[40] which includes diagnoses from both hospitalisations and

outpatient visits in specialised care. Diagnoses received during planned visits (i.e. follow-ups and referrals) were excluded from the analyses. Although this is a more conservative estimate of psychiatric disorders, this measure was used to avoid overestimation of diagnoses; the diagnosis that is the reason for treatment initiation is also coded during follow-ups and referrals, regardless of current symptoms. Sensitivity analyses including planned visits were also carried out. Psychiatric disorders included three diagnostic categories; psychoses (F20-F29), mood disorders (F30-F39), and anxiety disorders (F40-F45, F48).

Suicidal behaviour

Suicide attempts and suicides were defined as emergency inpatient or outpatient hospital visits or death due to intentional self-harm (X60-X84). Information on suicide attempts was collected from The Patient Register, and information on suicides was collected from the Cause of Death Register.[41]

Transport accidents and traffic offences

Transport accidents were defined as an emergency inpatient or outpatient hospital visit or death due to transport accidents (V00-V99). Traffic offences were defined as convictions or suspicions of traffic offences (defined as crimes against the road traffic offences act, and including reckless driving, unlawful driving, hit and run offences, causing death or injury by driving, and moving violations). Information on transport accidents was collected from the Patient Register and the Cause of Death Register. Information on convicted traffic offences was collected from the National Crime Register, and information on suspected traffic offences was extracted from the Register of Person Suspected of Offences.

Substance abuse

Information on alcohol abuse and dependence (ICD-9: 291, 303, 305A, 980; ICD-10: F10), drug abuse and dependence (ICD-9: 292, 304, 977W, 977X; ICD-10: F11-F16, F18-F19), and nicotine dependence (ICD 9: 305B; ICD-10: F17) was collected from the Patient Register.

Statistical analyses

Individuals were followed from November 22, 2006 to December 31, 2009. A between-individual Cox proportional hazards regression compared average rates of each outcome during varenicline medication for all individuals with rates during non-

medication for all individuals. In this analysis, follow-up period was split up into the period before the first outcome, periods between outcomes, and the period after the last outcome. Time at risk was measured from the start of each period, and medication was used as a time-varying covariate. Robust standard errors were calculated to account for correlations between periods within the same individual. Analyses were adjusted for sex and age in a second step.

The principal analyses were within-individual stratified Cox proportional hazards regression, with each individual entering as a separate stratum in the analysis and serving as his/her own control. Thus, the obtained hazard ratio is adjusted for (i.e. stratified on) all potential time-invariant confounders within each individual. To adjust for age, which is a time-varying potential confounder, age was added to the model as a time-varying covariate, with one factor for each whole year. Periods of treatment and non-treatment were adjusted for migration, imprisonment, institutional youth care, hospitalisation, and death. Migrations and deaths were identified by linking individuals to the Migration and Cause of Death Registers. Periods in prison and institutional youth care were accounted for by linkage to the Prison Register, and periods in hospitalisation were estimated using the Patient Register. In the within-individual stratified Cox proportional hazards regression, only individuals who change medication status contribute directly to the estimate. All other individuals contribute indirectly through the estimates of other covariates. Since the covariates in the within-individual stratified Cox proportional hazards regression are time-varying, we did not test for the proportional hazards assumption.

More information on this approach is provided in studies of ADHD medication, antipsychotics and mood stabilisers.[42-45] SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) was used in all analyses. The project was approved by the Ethics committee at Karolinska Institutet (2005/4:5).

Sensitivity analyses

In sensitivity analyses, each of the three diagnostic categories included in the definition of psychiatric disorders (i.e. mood disorders, anxiety disorders, and psychoses) was analysed separately. First, all individuals in the cohort were included in the analyses. Second, to test for confounding by pre-existing psychiatric disorders, only individuals with pre-existing psychiatric diagnoses (ICD-9: 295-302, 307-316; ICD-10: F20-F48, F50-F69, F90-F98, diagnosed before November 1, 2006) were

included. Third, only individuals without prior psychiatric disorders were included in the analyses. Furthermore, sensitivity analyses including both emergency and planned inpatient and outpatient visits for incidence of new psychiatric disorders were carried out.

RESULTS

Between 1 November, 2006 and 31 December, 2009, 43 861 women and 25 896 men were prescribed varenicline in Sweden (see Table 1 for background characteristics). In the medicated population, the highest rates for adverse outcomes were for suspected crimes (5.4%) followed by 4.6% who were diagnosed with a new psychiatric disorder during follow-up. There were lower rates of serious traffic-related incidents (1.4%) and suicidal behaviours that attracted medical care (0.9%)

Our unadjusted between-individual Cox proportional hazards regression showed that individuals with varenicline prescriptions demonstrated significantly increased hazards of a range of adverse outcomes. This included the incidence of new psychiatric disorders (hazard ratio [HR]=3.29, 95% confidence interval 2.99 to 3.63), of suicidal behaviour (HR=3.44, 2.64 to 4.47), of being suspected of a crime (HR=1.45, 1.30 to 1.62), and of being convicted of a crime (HR=1.18, 1.05 to 1.32) when compared to individuals who were not prescribed varenicline. Varenicline prescription was, however, not associated with significantly increased hazards of transport accidents or traffic offences. When adjusting for age and sex in the between-individual Cox proportional hazards regression, individuals with varenicline prescriptions demonstrated significantly increased hazards of all seven outcomes when compared to non-medicated individuals (Table 2).

In order to account for residual confounders that might explain the observed increased hazards, we then compared the rates of each outcome within the same individual (i.e. with each individual serving as his or her own control), using the within-individual design. This showed that being prescribed varenicline was not associated with significantly increased hazards of suspected or convicted crimes, suicidal behaviour, transport accidents, or suspected or convicted traffic offences (Table 2). However, varenicline was associated with an increased hazard of incidence of new psychiatric disorders (HR=1.18, 1.05 to 1.31).

To further examine the associations between varenicline and incidence of new psychiatric disorders, each diagnostic category was analysed separately (Table 3). Results from the within-individual analyses showed that varenicline was associated with increased hazards of anxiety (HR=1.27, 1.06 to 1.51) and mood (HR=1.28, 1.07 to 1.52) disorders. However, associations were not significant for psychoses.

To test for confounding by pre-existing psychiatric disorders, we restricted analyses to individuals diagnosed with pre-existing psychiatric disorders (n=493 927),

and to individuals without prior psychiatric disorders (n=7 423 509), respectively. Results from the within-individual analyses showed increased hazards of mood and anxiety disorders only for individuals with pre-existing psychiatric disorders (Table 3). Furthermore, since a more conservative measure of incidence of new psychiatric disorders (i.e. excluding all follow-ups and referrals) had been used in all the above analyses, sensitivity analyses were carried out where emergency visits as well as follow-ups and referrals were included. Results from these sensitivity analyses showed similar disorders being significantly associated with varenicline, but with lower effect sizes: increased hazards for anxiety (HR=1.08, 1.00 to 1.16) and mood disorders (HR=1.09, 1.03 to 1.16), but not for psychoses (HR=1.07, 0.96 to 1.19).

DISCUSSION

Main findings

Varenicline is widely prescribed for the treatment of nicotine dependence.[5 6] Previous research on varenicline has been inconsistent with regards to adverse events, including suicidality, violence, and incidence of new psychiatric disorders.[11-28] We used a large population-based cohort of nearly 8 million individuals, in whom 69 757 were treated with varenicline between 2006 and 2009, and investigated associations with adverse events. Our crude between-individual analyses, which did not account for any confounding factors, estimated that individuals on varenicline had substantially increased hazards of incidence of new psychiatric disorders and suicidal behaviour when compared to individuals who were not prescribed varenicline, and also had an elevated risk for criminal offending. In the next step, we adjusted for two known confounders for these outcomes; sex and age. These adjusted between-individual analyses showed that individuals on varenicline presented increased hazards of all seven adverse outcomes. In the third step, and our principal analytic strategy, we compared periods of medication to periods of non-medication within the same individual in order to control for confounding by indication. In these analyses, we found no associations for suicidal behaviour, suspected and convicted criminal offending, transport accidents, and suspected and convicted traffic offences. In addition, the hazard for incidence of new psychiatric disorders was substantially attenuated (from over 2 in the between-individual analyses to 1.2 in the within-individual study).

Strengths and limitations of the study

The current study is an improvement on prior observational studies through the use of a within-individual design that adjusts for both residual confounders and confounding by indication.[42-45] The study was characterised by several strengths, including a large population-based cohort with longitudinal data covering several outcomes. Furthermore, information on medication was complete as each prescription of varenicline that is collected at pharmacies is registered in the Prescribed Drug Register. Our results suggest that previously reported associations between varenicline and criminal offending, and suicidal behaviour are not causal.[9 16-18] Tobacco smokers are more likely to be aggressive and impulsive, and have higher

rates of suicidal behaviour,[46-49] thus, prior associations are likely to have been confounded by unmeasured factors. This underscores the point that post-marketing surveillance reports are subject to over-reporting and confounding by indication,[29 50] and the need to triangulate data on adverse effects of medication using different designs.

Our study is the first, to our knowledge, to examine associations with transport accidents and traffic offences. Previously, traffic accidents have been reported as a 'strong signal' in post-marketing surveillance events reported to the FDA.[51] We found no suggestion of a causal association between varenicline and transport accidents and traffic offences in the within-individual analyses. Thus, the signal identified in post-marketing surveillance data may reflect overall higher rates of traffic accidents among smokers.[52 53]

Our negative findings are mostly in line with RCT data,[20-23 28] and our findings have extended prior RCTs by examining associations in a large cohort sufficiently powered to detect rare events,[32-35] by studying a wide range of adverse outcomes, and by separately examining those with pre-existing psychiatric diagnoses. The one inconsistency with previous RCTs is that we found small but statistically significant associations with the incidence of new psychiatric disorders. When explored further, we found no clear association for psychoses, suggesting that previous case reports on varenicline-induced psychoses were not causal.[11-15] However, the risk remained for anxiety (HR=1.27, 1.06 to 1.51) and mood (HR=1.28, 1.07 to 1.52) disorders. When stratifying on psychiatric history, there was no apparent difference. The within-individual analysis, however, did not take time-varying confounding factors into account, i.e. factors that were associated with both the onset of varenicline treatment and the outcome. The increased risk of mood and anxiety disorders during varenicline treatment in this group could thus be caused by time-varying factors other than varenicline, including smoking cessation. When deprived of nicotine, nicotine-dependent individuals can produce withdrawal symptoms that include depression and anxiety as nicotine includes psychoactive compounds that mimic MAO-inhibiting antidepressant effects. [54 55] It has been argued that varenicline is highly selective for a4b2 nicotinic receptors, and at therapeutic levels does not bind to other neurotransmitter receptors and transporters, including those implicated in mental health problems.[54 56] The associations reported here should thus be regarded with caution, and need confirmation in further studies.

In addition to the lack of information on time-varying covariates, other limitations include the use of official registers, which underestimate true rates of most outcomes; only outcomes serious enough to warrant emergency visits or hospitalisations (for psychiatric disorders, traffic accidents or suicidal behaviours), or detection by the police (for crime outcomes), would end up in the registers. On the other hand, register-based outcomes are more comparable across countries than self-reports and represent important public health concerns. Furthermore, although our data on collected medication is complete, it is unable to account for lack of, or variations, in adherence. This problem is parallel to non-adherence in RCTs, and our within-individual estimate is comparable to the intention-to-treat analysis used in RCTs. Finally, our study was conducted in Sweden, a country with a relatively low prevalence rate of daily smokers in international comparisons,[57] with an average of 14% of adult daily smokers as compared to the average of 23% of adult daily smokers in the EU.[58] Differences in smoking rates, as well as in varenicline prescriptions, may thus affect the generalisability of results. Nevertheless, our findings in relation to suicidal outcomes are in line with cohort studies using different designs from the UK,[24 27] and Denmark.[26]

Conclusions and implications for further research

In summary, our results provide no evidence for a causal association between varenicline and incidence of criminal offending, suicidal behaviour, transport accidents, traffic offences, and psychoses. However, an increased risk of mood and anxiety disorders during periods of varenicline medication was found, which requires confirmation using other study designs.

What is already known on this topic

Varenicline is widely prescribed for the treatment of nicotine dependence, but reports of suicidality, depression, psychoses and violence have emerged, leading to warnings issued by regulatory agencies in Europe and the US.

Varenicline use has also been restricted or prohibited for several transportation industry professions, including pilots, air traffic controllers, truck and bus drivers, and certain military personnel due to reports of traffic accidents.

Research on the safety of varenicline, however, is not clear; results from post-marketing surveillance studies and case reports are not consistent with observational data and randomised controlled trials.

What this study adds

This study used a large population-based cohort with longitudinal data covering several outcomes.

A within-individual design was used, where selection effects can be minimised, and unknown confounders and confounding by indication can be adjusted for.

Our results provided no evidence for a causal association between varenicline and criminal offending, suicidal behaviour, transport accidents, traffic offences, or psychoses. However, an increased risk of mood and anxiety disorders was found, which requires confirmation using other study designs.

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Transparency declaration

Yasmina Molero affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Contributors

YM was involved in the conception of the study, analysis and interpretation of the data, and writing the manuscript. SF was involved in the conception of the study, interpretation of the data, and writing the manuscript. JZ was involved in the study design and analysis and interpretation of the data. PL and CHG were involved in study conception and interpretation of the data. All authors were involved in revising the article critically for important intellectual content and final approval of the version to be published. SF is the guarantor.

Ethical approval

This study was approved by the ethical committee of Karolinska Institutet (2005/4:5).

Data sharing

No additional data available.

REFERENCES

1 Shafey O, Dolwick S, Guindon GE (eds). Tobacco Control Country Profiles 2003, American Cancer Society, Atlanta, GA, 2003. Available at: http://www.who.int/tobacco/global_data/country_profiles/en/ Accessed December 23, 2014

2 Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380: 2224-60.

3 World Health Organisation. Global health risks: mortality and burden of disease attributable to selected major risks, 2009.

4 Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database of Systematic Reviews* 2013, Issue 5.

5 Food and Drug Administration (FDA). FDA drug safety communication: Safety review update of Chantix (varenicline) and risk of neuropsychiatric adverse events. October 24, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm276737.htm Accessed December 23, 2014.

6 National Institute for Health and Clinical Excellence. NICE implementation uptake report: smoking cessation drugs, 2010.

7 FDA. FDA press release: FDA issues public health advisory on Chantix. February 2, 2008. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116849.htm Accessed December 23, 2014.

8 Medicines and Healthcare products Regulatory Agency (MHRA). Varenicline: possible effects on driving; psychiatric illness. *Drug Safety Update* 2007;1:12.

9 Moore TJ, Furberg CD, Glenmullen J, Maltsberger JT, Singh S. Suicidal behavior and depression in smoking cessation treatments. *PLoS ONE* 2011;6: e27016.

10 Kuehn BM. Varenicline Gets Stronger Warnings About Psychiatric Problems, Vehicle Crashes. *JAMA* 2009;302:834.

11 Annagur BB, Bez Y. Varenicline-induced psychotic depressive episode in a patient with bipolar disorder. *Ther Adv Psychopharmacol* 2012; 2:35–37.

12 Cinembre B, *Akdag ST, Metin O, Doganavsargil O.* Varenicline-induced psychosis. *CNS Spectr*. 2010;15:469-72.

13 DiPaula BA, Thomas MD. Worsening psychosis induced by varenicline in a hospitalized psychiatric patient. Pharmacotherapy 2009;29:852–57.

14 Forcen FE, Martinez FL, Moya AM. Varenicline precipitating psychosis in a patient with no previous psychiatric history: A case report of a Spanish patient who was later diagnosed with paranoid personality disorder. *Clin Schizophr Relat Psychoses* 2012;5:221-3.

15 Gupta A, Bastiampillai T, Adams M, Nelson, A, Nance, M. Varenicline induced psychosis in schizophrenia. *Aust N Z J Psychiatry* 2012;46:1009.

16 Aagaard L, Hansen EH. Adverse drug reactions reported by consumers for nervous system medications in Europe 2007 to 2011. *BMC Pharmacol Toxicol* 2013;14:30.

17 Harrison-Woolrych M, Ashton J. Psychiatric adverse events associated with varenicline. An intensive postmarketing prospective cohort study in New Zealand. Drug Saf 2011; 34: 763-72.

18 Moore TJ, Glenmullen J, Furberg CD. Thoughts and acts of aggression/violence toward others reported in association with varenicline. *Ann Pharmacother* 2010;44:1389-94.

19 Meyer, TE, Taylor LG, Xie S, Graham DJ, Mosholder AD, Williams JR et al. Neuropsychiatric events in varenicline and nicotine replacement patch users in the Military Health System. Addiction 2013;108:203-10.

20 Cincipirini *PM, Robinson JD, Karam-Hage M, Minnix JA, Lam C, Versace F.* Effects of varenicline and bupropion sustained-release use plus intensive smoking cessation counseling on prolonged abstinence from smoking and on depression, negative affect, and other symptoms of nicotine withdrawal. *JAMA Psychiatry 2013;70:522-33.*

21 Foulds J, Russ C, Yu C-R, Zou KH, Galaznik A, Franzon M, et al. Effect of varenicline on individual nicotine withdrawal symptoms: a combined analysis of eight randomized, placebo-controlled trials. *Nicotine Tob Res* 2013;15:1849-57.

22 Garza D, Murphy M, Tseng L-J, Riordan HJ, Chatterjee A. A double-blind randomized placebo-controlled pilot study of neuropsychiatric adverse events in

abstinent smokers treated with varenicline or placebo. *Biol Psychiatry* 2011;69:1075–82.

23 Gibbons RD, Mann JJ. Varenicline, smoking cessation, and neuropsychiatric adverse events. *Am J Psychiatry* 2013;170:1460-7.

24 Gunnell D, Irvine D, Wise L, Davies C, Martin RM. Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. *BMJ* 2009;339:b3805.

25 Nahvi, S., Wu B, Richter KP, Bernstein SL, Arnsten JH. Low incidence of adverse events following varenicline initiation among opioid dependent smokers with comorbid psychiatric illness. *Drug Alcohol Depend* 2013;132:47-52.

26 Pasternak B, Svanström H, Hviid A. Use of varenicline versus bupropion and risk of psychiatric adverse events. *Addiction* 2013;108:1336–43.

27 Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. *BMJ* 2013;347:f5704.

28 Tonstad S, Davies S, Flammer M, Russ C, Hughes J. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline. A pooled analysis. *Drug Saf* 2010;33:289-301.

29 Gibbons RD, Amatya AK, Brown CH, Hur K, Marcus SM, Bhaumik DK, Mann JJ. Post-approval drug safety surveillance. *Annu Rev Public Health* 2010;31:419–37.

30 Kalman D, Baker Morissette S, George TP. Co-morbidity of smoking in patients with psychiatric and substance use disorders. *Am J Addict* 2005;14:106-23.

31 Kuehn BM. New reports examine psychiatric risks of varenicline for smoking cessation. *JAMA* 2012:307:129-130.

32 Kishi T, Iwata N. Varenicline for smoking cessation in people with schizophrenia: systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci* 2014;Oct 5. [Epub ahead of print].

33 Chengappa KN, Perkins KA, Brar JS, Schlicht PJ, Turkin SR, Hetrick ML, et al. Varenicline for smoking cessation in bipolar disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2014;75:765-72.

34 Anthenelli RM, Morris C, Ramey TS, Dubrava SJ, Tsilkos K, Russ C, et al.

Effects of varenicline on smoking cessation in adults with stably treated current or past major depression: a randomized trial. *Ann Intern Med* 2013;159:390-400.

35 Evins AE, Cather C, Pratt SA, Pachas GN, Hoeppner SS, Goff DC, et al. Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. *JAMA* 2014;311:145-54.

36 Wettermark B, Hammar N, MichaelFored C, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register – Opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007;16:726–35.

37 Hays JT, Ebbert JO. Varenicline for tobacco dependence. *N Engl J Med* 2008;359:2018–24.

38 National Council for Crime Prevention. *Kriminalstatistik 2010 [Criminal statistics 2010].* Västerås: National Council for Crime Prevention.

39 Fazel S, Grann M. The population impact of severe mental illness on violent crime. *Am J Psychiatry* 2006;163(8):1397-1403.

40 Ludvigsson J, Andersson E, Ekbom A, Feychting M, Kim J-L, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450.

41 Johansson LA, Westerling R. Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. *Int J Epidemiol* 2000;29:495–502.

42 Chang Z, Lichtenstein P, D'Onofrio BM, Sjölander A, Larsson H. Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: a population-based study. *JAMA Psychiatry* 2014;71:319-25.

43 Chen Q, Sjolander A, Runeson B, D'onofrio BM, Lichtenstein P, Larsson H. Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. *BMJ* 2014;348:g3769.

44 Fazel S, Zetterqvist J, Larsson H, Långström N, Lichtenstein N. Antipsychotics, mood stabilisers, and risk of violent crime. *Lancet* 2014;S0140-6736:60379-2.

45 Lichtenstein P, Halldner L, Zetterqvist J, Sjölander A, Serlachius E, Fazel S, et al. Medication for Attention Deficit-Hyperactivity Disorder and criminality. *New Engl J Med* 2012;367:2006–14.

46 Baek J-H, Eisner L-R, Nierenberg AA. Smoking and suicidality in subjects with major depressive disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Affect Disord* 2013;150:1158-66.

47 Dakwar E, Popii M, Coccaro EF. Lifetime history of cigarette smoking associated with aggression and impulsivity in both healthy and personality disordered volunteers. *J Pers Disord* 2011;25:645-55.

48 Holma IA, Holma KM, Melartin TK, Ketokivi M, Isometsa ET. Depression and smoking: a 5-year prospective study of patients with major depressive disorder. *Depress Anxiety* 2013; 30:580-8.

49 Schneider B, Lukaschek K, Baumert J, Meisiner M, Erazo, Ladwig K-H. Living alone, obesity, and smoking increase risk for suicide independently of depressive mood findings from the population-based MONICA/KORA Augsburg cohort study. *J Affect Disord* 2014;152-154:416-21.

50 Mayet A, Nivoix P, Haus-Cheymol R, De Laval F, Verret C, Duron S, et al. Increase in reported adverse events following seasonal influenza vaccination among the French armed forces, 2008-2009: possible role of stimulated reporting and background cases of influenza-like infection. Public Health. 2012;126:70-6.

51 Institute of Safe Medicine Practices. Strong safety signal seen for new varenicline risks. May 21, 2008. Available at: http://www.ismp.org/docs/vareniclinestudy.asp Accessed December 23, 2014.

52 Yiengprugsawan V, Berecki-Gisolf J, Bain C, et al. McClure R, Seubsman S-A, Sleigh AC. Predictors of injury mortality: findings from a large national cohort in Thailand. *BMJ Open* 2014;4:e004668.

53 Wen CP, Tsai SP, Cheng TY, Chan HT, Chung WS, Chen CJ. Excess injury mortality among smokers: a neglected tobacco hazard. *Tob Control* 2005;14Suppl1:i28-32.

54 Hughes JR. Smoking and Suicide: A Brief Overview. *Drug Alcohol Depend* 2008;98:169–178.

55 Ahmed AI, Ali AN, Kramers C, Härmark LV, Burger DM, Verhoeven WM. Neuropsychiatric Adverse Events of Varenicline. A Systematic Review of Published Reports. *J Clin Psychopharmacol* 2013;33:55Y62.

56 Kaur K, Kaushal S, Chopra SC. Varenicline for smoking cessation: A review of the literature. *Curr Ther Res Clin Exp* 2009;70:35-54.

57 Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B et

al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. *JAMA* 2014;311:183-92.

58 OECD. Health at a glance: Europe 2012, OECD Publishing. 2012. Available at: http://dx.doi.org/10.1787/9789264183896-en. Accessed December 23, 2014.

Table 1. Descriptive data of varenicline cohort and non-medicated cohort in Sweden over 2006-2009

	Varenicline cohort	Non-medicated cohort[§]
N	69757	7847679
Characteristics at baseline 2006		
Sex (%)		
Women	43861(62.9)	3964263 (50.5)
Men	25896 (37.1)	3883417 (49.5)
Age distribution (%)		
< 20	408 (0.6)	982116 (12.5)
20-29	3744 (5.4)	1084733 (13.8)
30-39	9226 (13.2)	1222610 (15.6)
40-49	17375 (29.9)	1221021 (15.6)
50-59	21480 (30.8)	1170086 (14.9)
60-69	14447 (20.7)	1022055 (13.0)
> 70	3077 (4.4)	1143656 (14.6)
Psychiatric diagnoses		
Pre-existing psychiatric diagnosis[∞]	9391 (13.5)	484536 (6.2)
Life-time alcohol abuse diagnosis[‡]	5562 (8.0)	197988 (2.5)
Life-time drug abuse diagnosis[‡]	2633 (3.8)	80535 (1.0)
Life-time nicotine dependence diagnosis[‡]	2379 (3.4)	19392 (0.3)
Characteristics during follow-up (November 22, 2006 to December 31, 2009)		
In-patient or out-patient care (%)		
Incidence of new psychiatric disorders	3213 (4.6)	168869 (2.2)
Anxiety disorders	1816 (2.6)	88905 (1.1)
Mood disorders	1717 (2.5)	84931 (1.1)
Psychoses	320 (0.5)	24384 (0.3)
Suicidal behaviour	657 (0.9)	26093 (0.3)
Crimes (%)		

Convicted of any crime	2256 (3.2)	204508 (2.6)
Suspected of any crime	3782 (5.4)	311914 (4.0)
Transport accidents and traffic offences (%)		
Traffic accident	989 (1.4)	108612 (1.4)
Convicted of a traffic offence	328 (0.5)	36271 (0.5)
Suspected of a traffic offence	440 (0.6)	46572 (0.6)

§ Non-medicated cohort; all individuals in the cohort who were not medicating with varenicline during follow-up.

∞ Diagnosed before November 1, 2006.

‡ Diagnosed between January 1, 1987 and December 31, 2009

Table 2. Associations between varenicline and adverse outcomes using unadjusted and progressively more adjusted analyses.

	No of events within-individual level /No of events between-individual level	Between-individual, unadjusted	Between-individual, adjusted for sex and age	Within-individual
		HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
Incidence of new psychiatric disorders	6910 / 337393	3.29 (2.99-3.63)	2.78 (2.63-2.93)	1.18 (1.05-1.31)
Suicidal behaviour	1077 / 40595	3.44 (2.64-4.47)	4.06 (3.12-5.28)	1.00 (0.72-1.37)
Suspected of any crime	6873 / 507823	1.45 (1.30-1.62)	2.33 (2.08-2.60)	1.10 (0.97-1.24)
Convicted of any crime	3252 / 338608	1.18 (1.05-1.32)	1.88 (1.68-2.11)	0.96 (0.79-1.16)
Transport accidents	1129 / 124445	1.05 (0.87-1.28)	1.46 (1.20-1.78)	1.01 (0.69-1.47)
Suspected of a traffic offence	772 / 99895	1.17 (0.88-1.55)	1.74 (1.31-2.32)	1.24 (0.84-1.84)
Convicted of a traffic offence	483 / 57068	1.13 (0.84-1.52)	1.81 (1.34-2.44)	1.30 (0.77-2.20)

Note: within-individual model compares the rate of adverse events when individuals are prescribed varenicline with the rate when the same individual is not prescribed varenicline.

Table 3. Associations between varenicline and incidence of certain psychiatric disorders stratified by pre-existing illness using within-individual models.

	No of events	All individuals	Individuals with pre-existing psychiatric disorders	Individuals without pre-existing psychiatric disorders
		HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
Anxiety disorders	3128	1.27 (1.06-1.51)	1.23 (1.01-1.51)	1.41 (0.99-2.00)
Mood disorders	3166	1.28 (1.07-1.52)	1.31 (1.06-1.63)	1.17 (0.86-1.60)
Psychoses	1129	0.94 (0.73-1.20)	0.90 (0.70-1.16)	3.52 (0.81-15.27)