Varenicline versus nicotine replacement therapy for long-term smoking cessation: an observational study using the Clinical Practice Research Datalink

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Scientific summary

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Scientific summary

Background

Smoking is the major avoidable cause of preventable morbidity and mortality in the UK and internationally. Smoking is also the principal cause of health inequalities and is responsible for most of the difference in healthy life expectancy between the richest and poorest in our society and those with and without mental health problems. Studies have estimated that smoking-related illnesses cost the NHS approximately £5B per year. Varenicline is the most clinically effective smoking cessation medicine for short-term abstinence in randomised controlled trials. However, there is relatively little evidence for its long-term effectiveness and impact on clinical outcomes that are relevant to the NHS.

Concerns have been raised that varenicline is associated with a higher risk of adverse events, particularly psychiatric morbidity, including suicide, self-harm and cardiovascular events, than other smoking cessation interventions. These concerns led the Food and Drug Administration to issue black box warnings about the possible adverse effects of varenicline from July 2009 to December 2016. The Medicines and Healthcare products Regulatory Agency also issued warnings; however, the observational studies that provided most of the evidence about the potential adverse effects of varenicline are prone to residual confounding. To address this gap in the literature, we investigated the adverse and beneficial effects of prescribing varenicline and nicotine replacement therapies using three statistical approaches to overcome confounding: multivariable-adjusted regression, propensity score regression and instrumental variable analysis.

We investigated the effects of varenicline on all-cause mortality and smoking abstinence, as well as on all-cause primary and secondary care use because smoking increases morbidity and imposes major costs on health-care services. We examined differences in smoking cessation medication effectiveness by socioeconomic position because a systematic review reported that NHS stop-smoking services might be helping to reduce inequalities in smoking prevalence by preferentially targeting smokers of lower socioeconomic position.

Objectives

- To investigate the long-term smoking abstinence of patients prescribed either varenicline or nicotine replacement therapies in the Clinical Practice Research Datalink and whether or not the effects differ by area-level deprivation.
- To investigate the causal effects of prescribing smoking cessation therapies on:
  - all-cause mortality and death due to chronic lung disease, lung cancer, coronary heart disease, pneumonia, cerebrovascular disease, diabetes and external causes
  - all-cause and incident cause-specific hospitalisation (specifically chronic lung disease, lung cancer, coronary heart disease, pneumonia, cerebrovascular disease, diabetes and external causes)
  - frequency of general practice and hospital attendance
  - incident primary care diagnosis of respiratory illness
  - incident primary care diagnosis of myocardial infarction
  - incident primary care diagnosis of depression or anxiety
  - weight in kg
  - incident registration of (1) any malignant neoplasm and (2) lung malignancy.
Methods

The data
We used an extract of data from the Clinical Practice Research Datalink. This data set is a nationally representative database of electronic medical records in the UK.

Data extraction
We extracted all smokers aged ≥ 18 years who were prescribed smoking cessation treatment [see Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press. URL: www.medicinescomplete.com (accessed January 2020), chapter 4.10.2] in ‘up to standard’ primary care centres contributing to the Clinical Practice Research Datalink after introduction of varenicline in the UK on 1 September 2006. Up to standard practices are practices that provided consistent data to the Clinical Practice Research Datalink. Inclusion criteria included having an ‘acceptable’ record and having at least 1 year of registration at their practice before their first smoking cessation prescription to allow for high-quality assessment of confounders. Patients’ records are defined as acceptable for research purposes if they registered with a practice with valid data, including on sex and age. There were 220,136 eligible patients.

Intervention
The intervention was the first prescription of varenicline within the eligible period, and the control treatment was nicotine replacement therapy. We focus on the first recorded treatment because subsequent treatment decisions are likely to be highly non-random.

Follow-up
Follow-up started on the date of the first prescription and ended on an event or the end of follow-up owing to mortality or end of registration.

Outcomes
We assessed each outcome at 3, 6, 9, 12, 24 and 48 months after the first prescription.

Smoking cessation
We defined smoking cessation using general practitioner records that indicated the patients’ smoking status. Each patient had multiple records that stated their smoking status, which can be indicated as current, former or never smoker. General practitioners were incentivised to record their patients’ smoking status.

Mortality
We defined mortality using the linked Office for National Statistics mortality data. This data set gave the date and primary causes of death. We investigated the following secondary outcomes: mortality due to chronic lung disease [International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes = J40–44], lung cancer (ICD-10 code = C34), coronary heart disease
Hospitalisation

We identified episodes of hospitalisation using the linked Hospital Episode Statistics data set. This data set provides the date and cause of hospitalisation for all linked patients. We investigated both all-cause hospitalisation and cause-specific hospitalisation using the codes described above for mortality.

Primary care diagnosis and attendance

Primary care diagnoses of myocardial infarction, chronic obstructive pulmonary disease, depression and anxiety were identified using validated code lists. The frequency with which each patient attended primary care was identified from their records.

Weight

The patients’ weight in the months following treatment was identified using their electronic medical records.

Diagnosis of depression or prescriptions for anxiety

Subsequent diagnosis of depression and prescriptions for hypnotics or anxiolytics were identified using diagnosis codes and prescription records in the 4 years after their first prescription.

Potential confounders

The potential confounders measured at baseline were age; body mass index; alcohol drug misuse, defined using Read codes; socioeconomic position measured by the Index of Multiple Deprivation; an indicator for having more than five primary care consultations in the year before first prescription; indicators for year of prescription; any previous prescriptions of hypnotics; any previous prescriptions of antipsychotics; any previous prescriptions of antidepressants; diagnoses of self-harm; diagnoses of myocardial infarction; diagnoses of chronic obstructive pulmonary disease; any psychiatric disease; and any serious comorbidity (a non-zero Charlson Comorbidity Index). We accounted for missing data by using imputation by chained equations, because some patients were missing body mass index and socioeconomic position data.

Statistical methods

We estimated the effects of varenicline and nicotine replacement therapy using three statistical methods: multivariable-adjusted logistic regression, propensity score matched regression and instrumental variable regression. We did not use Cox survival models because the proportional hazards assumption did not hold. Our basic adjusted models adjust for sex, year of first prescription and age. Our fully adjusted results also adjust for all confounders described above. We used propensity score and the covariates described above to match patients treated with varenicline to other similar patients prescribed nicotine replacement therapy using one-to-one matching with no calliper. There was a complete overlap in the propensity scores between patients prescribed varenicline and nicotine replacement therapy. The propensity score depends on similar assumptions to multivariable-adjusted regression (conditional
exchangeability). Both approaches could suffer from residual confounding. We used instrumental variable analysis to address this residual confounding.

Instrumental variable analysis requires a variable, the ‘instrument’ that is defined by three assumptions: that the instrument (1) associates with the treatment of interest, (2) is not associated with observed or unobserved potential confounding factors and (3) does not directly affect the outcome. A widely used instrument in pharmacoepidemiology is physicians’ prescribing preferences for different medications. We cannot directly measure general practitioners’ preferences, so we used the prescriptions to their previous seven patients seen before the index patient as a proxy for their preferences. We investigated whether or not the instrumental variable assumptions held by (1) testing the association of their prior prescription with their subsequent prescriptions and (2) investigating the association with potential confounders. We estimated the effects of varenicline and nicotine replacement therapy using additive structural models for binary outcomes and two-stage least squares for continuous outcomes.

All standard errors account for the clustering of patients at the practice level.

**Results**

We sampled 287,079 patients who were prescribed smoking cessation medications; of these, 70,610 patients received a varenicline prescription and 149,526 received a nicotine replacement therapy prescription. These patients were used to estimate the effect of smoking cessation medication on smoking cessation. A subset of 126,718 patients had data linked to the Hospital Episode Statistics data set, of whom 41,742 received a varenicline prescription and 84,976 received a nicotine replacement therapy prescription. On average, patients prescribed varenicline were healthier in almost every way than those prescribed nicotine replacement therapy. They were younger, less likely to have comorbidities or neuropsychiatric conditions and were less likely to be prescribed other medications. Our primary outcome was smoking cessation 2 years after the first prescription. In the full results, we present the estimates for 3, 6, 9, 12, 24 and 48 months. The results described in this summary all relate to 24 months after the first prescription.

**Smoking cessation**

Two years after their first prescription, 28.8% of patients prescribed varenicline had quit, compared with 24.3% of patients prescribed nicotine replacement therapy. After adjustment for sex, age and year of prescription, using multivariable regression, patients prescribed varenicline were 30% (95% confidence interval 27% to 33%) more likely than patients prescribed nicotine replacement therapy to be non-smokers at 2 years. This difference fell to 26% (95% confidence interval 23% to 29%) after adjustment for all the potential confounders. There was little evidence of differences by socioeconomic deprivation. The propensity score matched and instrumental variable regression suggested similar differences in effectiveness. These results are comparable to the effects observed in meta-analyses of randomised controlled trials. Our estimates suggested that 4.76 (95% confidence interval 2.77 to 6.74) additional patients would be expected to quit within 2 years per 100 patients prescribed varenicline rather than nicotine replacement therapy.

**Mortality**

Patients prescribed varenicline had lower mortality than those prescribed nicotine replacement therapy. For every 100 patients prescribed varenicline rather than nicotine replacement therapy, there were 1.33 (95% confidence interval 1.11 to 1.55) fewer deaths. This difference fell to 1.20 (95% confidence interval 0.97 to 1.44) after adjustment for baseline covariates using multivariable-adjusted regression.
Patients prescribed varenicline had lower cause-specific mortality, including 0.25 (95% confidence interval 0.16 to 0.33) fewer lung cancer deaths per 100 patients within 2 years of their first prescription. These differences modestly attenuated after adjustment for baseline covariates; however, the baseline differences between individuals could explain relatively little of the observed differences in mortality.

In contrast, there was little evidence from the instrumental variable analysis that patients prescribed varenicline had lower mortality (risk difference per 100 patients prescribed = -0.67, 95% confidence interval -1.46 to 0.11). There was little consistent evidence from the instrumental variable analysis of effects on cause-specific mortality. In particular, there were similar rates of lung cancer mortality (risk difference = 0.00, 95% confidence interval -0.27 to 0.26).

**Hospitalisation**

Patients prescribed varenicline were less likely to be hospitalised (risk difference = 6.33, 95% confidence interval 5.60 to 7.07). After adjustment for baseline covariates using multivariable-adjusted regression, this difference fell (risk difference = 1.20, 95% confidence interval 0.97 to 1.44). These differences were primarily due to chronic lung disease, pneumonia, cardiovascular disease and external causes. The instrumental variable estimates provided little evidence that varenicline reduced hospitalisation, but they were imprecise.

**Primary care diagnosis and attendance**

Patients prescribed varenicline were less likely to receive a primary care diagnosis of myocardial infarction or chronic obstructive pulmonary disease (risk difference = 0.14, 95% confidence interval 0.03 to 0.26, and 0.65, 95% confidence interval 0.35 to 0.94, respectively). The baseline covariates using multivariable-adjusted regression explained a proportion of these differences. The instrumental variable estimates provided little evidence that varenicline caused these reductions in diagnoses of myocardial infarctions and chronic obstructive pulmonary disease. Patients prescribed varenicline attended primary care 14.37% (95% confidence interval 12.19% to 16.50%) less frequently. This difference fell to 4.29% (95% confidence interval 3.31% to 4.73%) after adjustment for covariates using multivariable-adjusted regression. The instrumental variable analysis suggested that varenicline caused a 19.49% (95% confidence interval 11.11% to 27.09%) drop in primary care attendance.

**Weight**

Patients who were prescribed varenicline were 1.28 kg (95% confidence interval 0.92 to 1.63 kg) heavier 2 years after the first prescription than patients prescribed nicotine replacement therapy. This difference attenuated after adjustment for baseline covariates using multivariable-adjusted regression (mean difference = 1.06 kg, 95% confidence interval 0.84 to 1.29 kg). The instrumental variable analysis implied that varenicline caused a similar 1.14-kg (95% confidence interval 0.09 to 2.20 kg) increase in weight after 2 years.

**Limitations**

A limitation of this study is that we used observational data from electronic medical records and did not randomise individuals to treatment. This issue means that we cannot be certain that the assumptions on which our analysis depends hold. Furthermore, for many of the outcomes, we had a limited number of events and, thus, limited power and precision. This issue may have limited our ability to detect effects on the outcomes.
Conclusions and recommendations

Implications for health care
Patients who were prescribed varenicline were substantially more likely to be non-smokers up to 4 years later than those who were prescribed nicotine replacement therapy. These differences were robust across different statistical methods. However, we found relatively little evidence that patients prescribed varenicline had substantially improved health outcomes in the 4 years following their first prescription. There was some evidence from multivariable-adjusted regression of lower mortality and morbidity. However, our instrumental variable results suggest that this is likely to be because of residual confounding. The instrumental variable results were less precise than the multivariable-adjusted regression results. However, the results were inconsistent with the health improvements seen in the conventional analysis. Across all analyses, patients prescribed varenicline were more likely to experience weight gain and had lower subsequent primary care attendance.

Recommendations for future research
Varenicline is both efficacious, as indicated by randomised trials, and effective in real-world settings. In line with national prescribing trends, there is some evidence that prescribing of varenicline has fallen substantially over the period we studied. These trends may be because of concerns over the adverse event profile, or more likely because of the increasing prevalence of e-cigarettes and outsourcing of smoking cessation services to local councils. Further information is needed about the longer-term effects of smoking cessation. The vast majority of longer-term evidence of the effects of quitting smoking comes from observational studies. If healthier and more health-conscious people are more likely to attempt to quit smoking, then these studies may overstate the benefits of quitting. More research is needed about the reversibility of the health impacts of smoking, using research methods that can overcome residual confounding.

Trial registration
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This report

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