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REG STUDY PROTOCOL

TITLE (LONG)

VARENICLINE AND BUPROPION FOR SMOKING CESSATION: CARDIOVASCULAR AND NEUROPSYCHIATRIC SAFETY IN SMOKERS WITH AND WITHOUT CHRONIC OBSTRUCTIVE PULMONARY DISEASE: AN OBSERVATIONAL STUDY USING THE OPCRD

TITLE (SHORT)

Varenicline and bupropion OPCRD safety study

Research Protocol developed by Dr Colin Simpson, Asthma UK Centre for Applied Research, The University of Edinburgh for consideration by The Respiratory Effectiveness Group

[please submit REG study proposals / protocols to David Price and Alison Chisholm – david@respiratoryresearch.org and alison@effectivenessevaluation.org. Should the protocol be approved for funding, to enable REG to liaise with the Anonymised Data Ethics Protocols and Transparency (ADEPT) Committee in relation to ethical approval of the protocol, please also provide: Covering letter to ADEPT on headed paper; Completed ADEPT Application Form; CV for the Chief Investigator (Or summary CV)]

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ABBREVIATIONS

Chronic Obstructive Pulmonary Disease – COPD

National Institute of Health and Clinical Excellence (NICE)

NRT – Nicotine Replacement Therapy

LAY SUMMARY

Varenicline is an effective therapy to aid smoking cessation. However, its use is limited by continuing concerns about possible risks of serious adverse heart and psychiatric events. The aim of this study is to investigate whether use of varenicline is associated with such events.

We will use the validated OPCRD general practice dataset. This uses data from a national health-care system in which all members of the community have free and ready access to smoking cessation treatment.

The findings from this study will substantiate the results of previous studies that show that varenicline is not likely to increase the risk of self-harm or depression or any of a wide range of other poor patient outcomes. The findings on this study will have clear implication for the safety warnings for varenicline and for clinical practice. They may suggest an opportunity for physicians to prescribe varenicline more broadly, even for patients with comorbidities, thereby helping more smokers to quit successfully than do at present.
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AIM & OBJECTIVE

The aim of this study is to assess the safety of varenicline using data from OPCRD. Our primary research question is: is the use of varenicline or bupropion for smoking cessation compared with NRT associated with an increased risk of cardiovascular or neuropsychiatric events?

BACKGROUND & RATIONALE

The best treatment to help smokers quit smoking according to UK and international clinical guidelines is a combination of pharmacotherapy and behavioural support.[1-2] The most effective pharmacotherapies are bupropion, nicotine replacement therapy (NRT; such as nicotine gum and patch), and varenicline. Varenicline, a partial α4β2 nicotine acetylcholine receptor agonist, is the newest drug on the market; it was introduced in the UK in December 2006, and has been recommended by the National Institute of Health and Clinical Excellence (NICE) as a treatment option since July 2007.[3] Varenicline has been shown in experimental studies to be more effective than bupropion and nicotine patch in the general smoking population.[4-5] Furthermore, varenicline is the only drug with proven long-term efficacy in smokers with chronic obstructive pulmonary disease (COPD); a trial showed a four-fold increase in continuous abstinence over a period of 12 months in users of varenicline compared with placebo.[6] Other medications failed to prove

efficacy over a period longer than six months in this group of smokers.[7] Varenicline has become the most frequently prescribed smoking cessation medication after NRT in England.[8] However, the safety of this new drug is not well established.

Recent reports have raised concerns about the safety of varenicline with regard to cardiovascular and neuropsychiatric diseases. For example, a summary of findings from various studies found a small, but significantly increased risk of adverse cardiovascular events in users of varenicline.[9] Reports of depression and suicidal thoughts among people prescribed varenicline led the Medicines and Healthcare Products Regulatory Agency (MHRA) to issue a warning.[10] Recent studies conducted in the general smoking population did not find an increased risk of cardiovascular and neuropsychiatric events in varenicline users.[11-13]. Our recent study using the QResearch database did not find any associations, however we wish to replicate this study in OPCRD to investigate whether a. similar results are found and b. whether a more robust analysis can be performed using an instrumental variable approach.

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STUDY DESIGN, DATASET AND METHODOLOGY

We will conduct a retrospective cohort in all adult patients from OPCRD who used varenicline, bupropion, or a NRT between 1st January 2007 and current (to replicate our original study we will also carry out a sensitivity analysis using 30th June 2012 as our end date.

We will explore the use of an instrumental variable to account for confounding by indication. Physicians' prescribing preferences, based on physicians' previous prescriptions, have been shown to be potentially valid instruments for a number of medications including smoking cessation therapies. [14-16]

STUDY POPULATION

For the analysis of the safety of varenicline and bupropion the following inclusion criteria will apply:

- Prescription of either single varenicline, single bupropion, or a single NRT between 1 January 2007 and 30 June 2012 (for the replication of the study) and the latest date of data extraction from the database. The date of first prescription of one of these drugs will define the individual patient's entry date to the cohort. We chose the start date because varenicline was introduced to the UK market in December 2006.
- Aged 18 years and over. We will include only patients over the age of 18 because smoking cessation medicines are only licensed for use in adults.

The following exclusion criteria will apply:

- Use of one of the three smoking cessation drugs during 12 months prior to the start date of the study (i.e., in the period from 1 January 2006 to 31 December 2006) to assure enough washout of any adverse events from previous drug use.
- Prescription of a combination of smoking cessation drugs or another prescription of a smoking cessation drug during the six months follow-up after the patient's entry date to single out adverse events of the three distinct drugs.

- Patients with less than one year of CPRD records before their first recorded prescription to increase the quality of the data.

COMPARISON GROUP / CONTROLS

There are three exposure groups: (1) single varenicline, (2) single bupropion, and (3) single NRT (i.e. nicotine patch, inhaler, nasal spray, gum, sublingual tablet or lozenge), based on the drug they were first prescribed. The exposure category will be defined by this initial drug, and patients will be considered always exposed to the respective drug for the entire follow-up. The usual course of treatment is 12 weeks of varenicline, 9 weeks for bupropion and 8-12 weeks for NRT. Start of follow-up will begin for each patient on the date of the first prescription of the smoking cessation medication and will end after six months follow-up or when reaching the specific outcome of interest (i.e., a major psychiatric or cardiovascular event). This duration of follow-up takes account for the suggestion that adverse events from drug use may occur after the treatment finished. A sensitivity analysis on the impact of drug switching (from one treatment to another) will also be carried out.

OUTCOMES

We will consider separate major incident psychiatric and cardiovascular outcomes that occur during 6 months follow-up (based on appropriate Read codes for primary care and ICD codes for secondary care/HES data if available) for which a potential association with varenicline use has been suggested. Psychiatric outcomes include: (1) fatal and non-fatal intentional self-harm, (2) depressive disorder, and (3) bipolar disorder, (4) agitation, (5) suicidal ideation, (6) hostility/aggression, (7) hallucination, and (8) behavior change. Cardiovascular outcomes include: (1) ischaemic heart disease, (2) cerebral infarction, (3) heart failure, (4) peripheral vascular disease, and (5) cardiac arrhythmia. Previous recordings of psychiatric and cardiovascular events will be considered to account for confounding by indication. As secondary outcome, we will assess these events during 3 months follow-up.

COVARIATES

Individuals who are prescribed one therapy are likely to be different from those prescribed another and those who are not prescribed any treatment. An extensive list of individual-level and practice-level characteristics will be included as confounders in the analyses. These will be defined at base line and include age, sex, index of multiple deprivation, strategic health authority of the GP practice, COPD severity (according to MRC dyspnoea score), alcohol misuse, any recordings of the above mentioned psychiatric and cardiovascular diseases prior to the patient's entry date to the cohort, and number of GP visits during 12 months prior of the patient's entry date to the cohort.

SAMPLE SIZE AND POWER CALCULATION

Based on earlier research,[17] the estimated sample size of patients who received a prescription during the 5-year period of observation will be 660 for varenicline, 390 for bupropion, and 3800 for NRT, which will provide sufficient (at least 80%) statistical power for the planned analyses.

DATA AND STATISTICAL ANALYSIS

Confounding by indication is an important potential source of bias in a safety analysis using observational (i.e. non-randomised) data. This form of confounding means that patients who choose a certain treatment may differ in prognostic factors from patients who do not choose this treatment. In the current context, for example, patients using medication for smoking cessation (varenicline or bupropion) may differ from patients who try to stop smoking without medication. They may have been more exposed to tobacco and are therefore more at risk of cardiovascular events. In the current study, we will reduce the risk of confounding by indication, amongst others, by comparing users of varenicline or bupropion with users of NRT.

Kaplan-Meier survival curves will be generated and examined for the three exposure groups (varenicline, bupropion, or NRT). We will then use Cox proportional hazards regression models to assess the association between medication use and each of the above mentioned main outcome measures and will report hazard ratios with 95% confidence intervals, with days since start of treatment as the time scale. Hazard ratios will be calculated for varenicline and bupropion with NRT as a reference. The proportional hazards assumption will be assessed by a Wald test for the interaction between treatment status and the underlying time scale. Start of follow-up will begin for each patient on the date of the first prescription of the smoking cessation medication and will end after six months follow-up or when reaching the specific outcome of interest. Patients will be censored who died from causes other than the specific outcome, who left their practice, or reached the end of the study period (31 December 2012 and dataset extraction date). In order to further reduce the risk of confounding by indication we will adopt a non-parsimonious approach and include all available patient characteristics (as potential confounders) in the model.

We will use propensity score matching [18] as a different analytic approach to account for potential confounding by indication. In multiple logistic regression models medication (with varenicline vs. NRT as dependent variable in the first model and bupropion vs. NRT in the second model) will be regressed on the above mentioned potential confounders. The resulting predicted probability values for medication use will be used as propensity score. Each patient using varenicline and each patient using bupropion will be matched to a patient using NRT (or to two or more patients using NRT in case there are twice or three times as many NRT users) based on their propensity score. For both comparisons (propensity score matched varenicline vs. NRT and bupropion vs. NRT) separate Cox proportional hazards regression models will be used to assess the association between medication use and each of the above mentioned main outcome measures.

We propose to use as an instrumental variable physicians' preferences for particular smoking cessation therapies. This uses naturally occurring variation in likelihood of prescription, “the instrumental variable” or “instrument,” that is associated with the actual prescription but, unlike the actual prescription, is not associated with observed and unobserved confounding factors. Variation in drug prescribing associated with the instruments can provide unconfounded estimates of causal relationships between being prescribed a drug and an outcome, provided a set of assumptions are met.

We will use physicians' choice of smoking cessation prescribed to one or more of their previous patients as a proxy for their current preferences and hence as a surrogate instrumental variable for actual prescriptions. Thus, each patient's

physician will be defined as having higher or lower preferences for NRT, bupropion or varenicline among those first prescribed smoking cessation therapy. We will test whether physicians' prior prescriptions (as proxies for physicians' prescribing preferences) are valid instruments [15]. This approach has been used in a previous study investigating varenicline safety [17]. All analyses will be performed using R.

STEERING COMMITTEE INVOLVEMENT

The Asthma UK Centre for Applied Research (AUKCAR) has an independent advisory group, which oversees the activities of the Centre.

PATIENT INVOLVEMENT

AUKCAR has an active patient and public involvement group http://www.aukcar.ac.uk/public/. We will include this study as part of the portfolio of research that is scrutinised by our group.

LIMITATIONS OF STUDY DESIGN / ANALYSIS

Some variables of potential interest may not available in the OPCRD, this includes drug adherence or potential confounders such as previous or present levels of tobacco exposure. Drug adherence cannot be measured as we are unable to track drug dispensing or patient adherence to prescription. Tobacco exposure might be a confounding factor because it is a risk factor for cardiovascular or neuropsychiatric events and might be associated with type of smoking cessation drug. We will attempt to address this issue by including previous cardiovascular and neuropsychiatric events and a range of other smoking-related diseases, recorded at baseline, as potential confounders in our models. However, we do not have data for smoking cessation during follow-up to assess potential differences in effectiveness of the three drugs. Thus, we will be unable to fully disentangle the complex pathways between type of drug, serious adverse events being studied, and mediating factors of drug adherence and effectiveness in terms of smoking cessation.

DATA DISSEMINATION PLANS

We will publish our results in a peer-reviewed journal.

STUDY TEAM

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All authors conceived and designed the study, revised the protocol, and gave final approval of the version submitted.

ETHICS

We will seek ADEPT approval for use of the Optimum Patient Care Database.

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