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Prescribed drugs or medicines and bullous pemphigoid
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The association between prescription drugs and vaccines commonly prescribed to older people and bullous pemphigoid: a UK population-based study

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ABSTRACT

Introduction

Bullous pemphigoid (BP) is a serious skin disease that results in large painful blisters developing over the body and occurs most commonly in older people (over 70 years). Despite several comorbidities such as stroke and a threefold increase in mortality, BP remains under-researched. The cause of BP is unclear. The auto-immune process may be triggered by medicines such as diuretics, but current evidence mainly comprises case-reports and small hospital-based studies. Electronic healthcare records from the Clinical Practice Research Datalink (CPRD) provide an opportunity to conduct a large population-based study, representative of people with BP in the UK, to assess exposure to prescribed medicines. Early identification of BP and prompt withdrawal of suspect medicines may lead to BP remission and improve long-term patient outcomes, including quality of life. We aim to determine whether medicines/vaccines, prescribed for common conditions in older people, are associated with BP in the UK population. The objectives are:

i. To determine the adjusted odds ratio of developing BP per therapeutic group and class, and for multiple exposure (i.e. the use of more than one therapeutic group of medicine/vaccine during the observation period), for medicines/vaccines commonly prescribed to older people in the UK.

ii. To identify which of the above are less associated with risk of BP, giving clinicians/prescribers alternative treatment options.

iii. To identify additional medicines associated with BP using machine learning.

iv. To identify associations between combinations of medicines prescribed to BP patients using machine learning.

v. To describe patient characteristics of those at risk of BP, following medicine use, using machine learning.

Methods

A UK population-based nested case-control study using the CPRD to determine associations between identified medicines/vaccines and BP. BP cases will be matched to up to 4 controls (age, sex, GP practice) using incidence density sampling. Exposure: medicines/vaccines commonly prescribed for older people; antibacterial, medicine for the

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cardiovascular system, stroke, diabetes, dementia, and influenza vaccination in the year leading up to diagnosis. Outcome measures: the odds of BP per therapeutic group, per class, and individual medicine; (reference=no exposure). Analysis: multivariable conditional logistic regression adjusted for a priori confounders. Confounding by indication will be considered and different exposure criteria assessed. We will undertake exploratory association rule mining to identify individual and combinations of medicines prescribed prior to BP. We will conduct unsupervised machine learning cluster analysis to identify groups of patients with demographic and clinical characteristics and their associations with prescribed medicines linked to BP.

Discussion

This study will (i) provide greater awareness of the risk of drug-associated BP amongst specialist and non-specialist healthcare professionals and therefore may facilitate earlier diagnosis of BP; (ii) support withdrawal of suspect medicines and switching to alternatives, where available, to achieve earlier remission of BP.

Key words

Bullous pemphigoid, Pharmaco-epidemiology, Adverse drug reaction, Primary care

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INTRODUCTION

Background

Bullous pemphigoid (BP) is the most common autoimmune blistering disease of the skin and mucous membranes and typically occurs in older people (>70 years). It is a disease in which antibodies target self-proteins in the superficial layers of the skin, resulting in painful blistering lesions. In some cases, where large areas of skin are affected, it can result in large ulcers.[1] BP can last for several years and has a big impact on the quality of life of patients and their families.[2,3] For example, BP is intensely itchy which is debilitating and having ulcerated skin can result in infection and sepsis. There is currently no cure for BP.[1]

We have recently reported the incidence of BP in England to be 7.6 per 100,000 person-years overall in adults, but 68 per 100,000 person-years in the over 80s.[4] These figures are higher than previously reported. We have also recently reported that BP is associated with three-times the risk of death compared to the general population.[4] Mortality could be high either due to the disease itself or the complications of treatment. The standard treatment for BP has traditionally been oral corticosteroids which have severe side-effects such as diabetes mellitus and osteoporosis. Despite its debilitating nature, treatment-related morbidity, and high mortality, BP remains under-researched, probably due to its rarity. In particular, the cause of BP is unclear. For some patients it may be associated with commonly prescribed medicines that dysregulate the immune system. This association is unsurprising as BP is a disease of older people and they tend to be exposed to multiple medications.

Review of the existing literature

The aetiology of BP is unclear however there is some evidence that neurological conditions and use of certain medications may be risk factors for BP.[5,6,7] Two systematic reviews, very recently published, have investigated the association between medication use and bullous pemphigoid.[5,6] Liu et al. conducted a meta-analysis and included thirteen case-control studies, one cohort study, and one randomised clinical trial (RCT) with 285 884 participants.[6] Most of the studies were hospital-based. From the meta-analysis, authors report a significant association between the development of bullous pemphigoid and the prescribed use of aldosterone antagonists, dipeptidyl

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peptidase 4 inhibitors, anticholinergics, and dopaminergic medicines. For the case-control studies, use of aldosterone antagonists (pooled OR, 1.75; 95% CI,1.28-2.40), dipeptidyl peptidase 4 inhibitors (pooled OR, 1.92; 95% CI, 1.55-2.38), anticholinergics (pooled OR, 3.12; 95% CI, 1.54-6.33), and dopaminergic medicines (pooled OR, 2.03; 95% CI, 1.34-3.05) was associated with BP. The cohort study, by Douros al. found an increased risk of BP among patients receiving dipeptidyl peptidase 4 inhibitors (hazard ratio, 2.38; 95% CI, 1.16-4.88; P =.02).[8] The RCT found a higher occurrence of BP in patients with diabetes receiving linagliptin (0.2% in diabetes group vs 0% in the placebo group). The systematic review by Verheyden et al. included 170 publications for qualitative analysis, all of which were case reports or series.[5] A total of 89 medicines from nine diverse classes were implicated with drug induced bullous pemphigoid. Based on the temporal relationship with administration and withdrawal, recurrence with re-challenge, and the diagnostic certainty, the strongest evidence was for dipeptidyl peptidase 4 inhibitors, PD-/PD-L1 inhibitors, loop diuretics and penicillins. Studies that had presented vaccines were mainly in children.[5]

With regards to studies that have been conducted in the UK, only one study, by Lloyd-Lavery et al., has investigated the association between several medicines and BP but this was based in one specialised centre, included a small number of patients, and did not explore multiple exposures (i.e. the use of more than one group of medicine during the observation period).[9] Eighty-six BP patients and 134 controls were included. They reported only loop diuretics were used significantly more frequently by the BP patients (adjusted odds ratio, 3.8 [95% CI 1.5-9.7]). The authors adjusted for confounders and indications associated with BP. The study by Douros et al. mentioned above used the CPRD to conduct a cohort study among 168,774 patients initiating antidiabetic medicines between January 2007 and March 2018 in the UK.[8] During 711,311 person-years of follow-up, 150 patients were newly diagnosed with BP. Current use of dipeptidyl peptidase-4 inhibitors was associated with an increased risk of BP compared with current use of other second- to third-line antidiabetic medicine (adjusted hazard ratio, 2.21 [95% CI 1.45-3.38]). Their findings are consistent with those by Plaquevent et al. and Tanaka et al. who conducted hospital-based cohort studies in France and Japan, respectively.[10,11] Although methodologically robust, Douros et al.'s study looked at only one therapeutic group and did not consider multiple exposure.[8]

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Rationale

According to the current scientific literature there is a gap in understanding the association between medicine/vaccine exposure and the risk of BP at population-based level in the UK. Studies published to date in the UK have been case-reports or hospital-based. A population-based study will permit assessing the impact of multiple exposure and more precise results due to the large sample size as well as minimising selection and recall bias. Our research team have recently validated primary care diagnostic codes for BP and shown that they have high predictive value (>85%).[12] Given that BP is a disease of older people, we will primarily focus on medicines/vaccines prescribed for diseases commonly prescribed in this population.[13] This novel study will provide important and precise findings for healthcare professionals who manage people with BP in the UK.

Aims and objectives

In this study, we will look to see which medicines are associated with BP, in general. The objectives are:

i. To determine the adjusted odds ratio of developing BP per therapeutic group and class, and for multiple exposure (i.e. the use of more than one therapeutic group of medicine/vaccine during the observation period), for medicines/vaccines commonly prescribed to older people in the UK.

ii. To identify which of the above are less associated with risk of BP, giving clinicians/prescribers alternative treatment options.

iii. To identify additional medicines associated with BP using machine learning.

iv. To identify associations between combinations of medicines prescribed to BP patients using machine learning.

v. To describe patient characteristics of those at risk of BP, following medicine use, using machine learning.

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METHODS

Research plan overview

The project will consist of two workstreams. The first workstream will explore the association between medicines and vaccines commonly prescribed in older people, using the classical epidemiological approach. The second workstream will consist of a machine learning project which will validate the results of workstream 1 and may identify additional prescribed medicines which have an increased risk of BP and describe the association between medicines and the patient characteristics of those at risk of BP following medicine use. This methodology has been used in other clinical areas such as heart disease.[14,15]

Workstream 1: Classical epidemiological approach

In this part of the study, the Clinical Practice Research Datalink (CPRD) will be used to identify patients with BP (using an algorithm we have previously developed)[12] and determine the associations between the use of specific medicines/vaccinations and the risk of BP.

Data sources: The CPRD is one of the largest primary care research databases containing the medical records of over 16 million patients, from 1774 practices, in the UK (CPRD GOLD and AURUM, as of March 2021).[16] Data are broadly representative of the demographics of the UK population.[17] The data have a high validity of recorded diagnoses including for BP.[12,18]

Study design: Nested case-control study where cases and controls are identified within the CPRD cohort of over 16 million patients. Cases of BP that occur in the defined cohort will be identified (using validated BP diagnostic codes)[12] and, for each, a specified number (n=4) of matched controls (patients without BP diagnostic codes during the observation period) will be selected from among those in the cohort who have not developed the disease by the time of disease occurrence in the case. This design is appropriate for our research question as BP is an uncommon outcome.[4] Also, a nested case-control is appropriate for looking at multiple exposure and reduces recall bias and the uncertainty regarding the temporal sequence between exposure and disease onset.

Observation period: the observation period will commence on the latest of (i) the practice's up-to-standard (i.e. research ready) date or (ii) the patient's current

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registration date. The observation period will terminate on the earliest of (i) date of death, (ii) transferred out date, or (iii) the practice's last data collection date.

Study population: Incident cases of BP (age ≥18years) identified in primary care. We will include all age-groups as drug induced BP may occur at a younger age than spontaneous BP. Controls: Age, sex, and GP practice matched up to 5 controls (patients without BP) per BP case using incidence density matching. A pseudo-diagnosis date will be the diagnostic date of their matched BP case. The matched controls will have to be alive and contributing to the data at the time of the pseudo-diagnosis date.

Sample size: All available data from the CPRD will be used. As of March 2021, there are at least 13,000 incident patients with BP with at least one year of medical records prior to diagnosis in the CPRD. The latter is important to measure sufficient exposure to medicine/vaccine use. A ratio of 1:4 controls will be used as it has been established that this ratio is sufficient for a case-control study.[19] To detect a clinically important odds ratio of at least 1.3 for medicines with exposure prevalence of 2%, 12,618 cases are required. The calculations are conducted for a power of 90%, significance level of 1% and correlation of exposure between cases and controls of 0.1. The estimated total sample size will therefore be at least 65,000 patients (13,000 cases and 52,000 controls).

Exposure: At least one prescription (BNF chapter) for antibacterial medicine (5.1), medicine for the cardiovascular system (2, 2.2, 2.4, 2.5), stroke (2.9, 4.7), diabetes (6.1), dementia (4.11) and influenza vaccine (14.4.2); within one year prior to BP or pseudo-diagnosis.32 We will define 'therapeutic groups' by the pathology they treat e.g. cardiovascular, and 'classes' by mode or mechanism of action e.g. loop diuretic. We will identify 'classes' within each 'therapeutic group' that are not associated with an increased risk of BP, giving clinicians/prescribers alternative treatment options in drug-triggered cases. We may only include the influenza vaccine as we expect to not have the power to look at other vaccinations.

Confounders: Age and sex are associated with BP and could be associated with medication use.[20.21] Considering GP practice is important to control for differences between practices with regards to prescribing. As deprivation and ethnicity are associated with medication use and with BP they too will be considered a priori confounders.[4,22,23] When looking at the association between dementia medication

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and BP, we will consider confounding by indication as stroke and Parkinson's disease are risk factors for BP and could be associated with having dementia and therefore with dementia medication use.[7,24,25] Dementia is also a risk factor for BP but as the majority of people on antidementia medication will have dementia, we will not be able to investigate confounding by indication for dementia.[7] We will interpret the results considering this limitation.

Confounders will be accounted for by (i) the design, and (ii) the analysis:

i. The confounding factors accounted for in the study design are age, sex and GP practice. Up to 4 controls (patients without BP) per BP case will be identified using incidence density matching. We will use a ratio of 1:4 controls as it has been established that this ratio is sufficient for a case-control study.[19] For some of the older age groups, >90 years, it may not be possible to identify exactly 4 controls but previous work shows this will be uncommon (less than 4%).[4] A pseudo-diagnosis date for the controls will be the diagnostic date of the matched BP case. The matched controls will have to be alive and contributing to the data at the time of the pseudo-diagnosis date. Age, sex and GP practice are all available in the CPRD's patient file.

ii. The confounding factors accounted for by the analysis are: dementia, stroke, Parkinson's disease, multiple sclerosis, deprivation and ethnicity. We will identify whether patients have a diagnostic code for these conditions at least one year prior to their BP diagnosis and create a binary variable for these conditions. In the CPRD, deprivation is measured by the index of multiple deprivation (IMD) and is known to be complete in the CPRD however ethnicity may not be.[4] We will therefore assess the amount of missing data for ethnicity and if it is more than 5% we will undertake multiple imputation.[26] Deprivation and ethnicity will be included in each of the logistic regression models when assessing the association between each therapeutic group/class and vaccine use and BP. Presence of stroke or Parkinson's disease will be included when assessing the association between dementia medication use and BP.

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Data analysis

Descriptive statistics will be used to describe cases and controls in terms of exposure, co-morbidities known to be associated with BP (Parkinson's disease and stroke at least 1 year prior to BP diagnosis), deprivation and ethnicity. Univariable and multivariable conditional logistic regression adjusted for the a priori confounders will be used to assess the association between each therapeutic group/class and vaccine use and BP.

Sensitivity analyses:

Five sensitivity analyses will be performed to explore potential biases and ensure the robustness of the main analysis.

(i) To take into account the potential confounding effect of ethnicity and deprivation, each fully adjusted model included ethnicity and index of multiple deprivation for patients from English and HES-linked practices as only these practices have such data.

(ii) To take into account diagnostic delay, the cut-off point for the extraction of prescriptions was changed from one to two years prior to the index date. The reported diagnostic delay of BP varies between 6.1 months to 2.8 years.

(iii) To investigate the magnitude of protopathic bias, which is the initiation of treatment for the symptoms of the undiagnosed disease of interest, prescription data up to six months prior to the index or pseudo-diagnosis date were excluded. As BP is not a common condition it can be misdiagnosed or diagnosis may be delayed.

(iv) Skin infection, for which patients may be prescribed antibiotics, can occur before BP is diagnosed. We, therefore, adjusted for the latest skin infection within 6 months prior to the index date in the multivariable models.

(v) To adjust for informed presence bias (i.e., health-seeking behaviour), we included the number of consultations as a categorical variable in the multivariable analysis.

Missing data: The only variable where we envisage missing data is ethnicity. If more than 5% of the study population have missing ethnicity, we will use multiple imputation.

Multiple testing: As we will be conducting several logistic regression models we will use a significance level of 0.01 rather than 0.05. According to the Bonferroni rule, $p<0.01$ is

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sufficient where <50 hypothesis tests are conducted. We do not envisage conducting more than 50 hypothesis tests. If we do, the cut-off p-value will be adjusted accordingly.

Feasibility counts

We have conducted feasibility counts in the CPRD to determine the percentage of cases with a prescription for medicines/vaccines commonly prescribed to older people. There are sufficient cases exposed to medicines/vaccines within the therapeutic groups mentioned above (i.e.>2% for classes within each therapeutic group), between 2 and 12 months prior to diagnosis. This time frame was chosen based on the systematic review by Verheyden et al.[5]

Workstream 2: Machine learning approach

In this part of the study, we will undertake exploratory association rule mining to identify individual and combinations of medicines prescribed prior to BP. We will also conduct unsupervised machine learning (ML) cluster analysis to identify groups of patients with particular demographic and clinical characteristics and their associations with prescribed medicines linked to BP.[14,15] This workstream will allow us to validate the results of workstream 1 and find additional findings.

Data source: CPRD

Study design, observation period, population, and controls: As in workstream 1.

Exposure: Medicines listed in Workstream 1 and other medicines (BNF Chapter) commonly prescribed in older people that have not been considered in Workstream 1: Constipation and bowel cleansing (1.2), Dyspepsia (1.4.1), Gastric and duodenal ulceration (1.4.2), Gastro-oesophageal reflux disease (1.4.3), Obstructive airway disease (3.1), Epilepsy and other seizure disorders (4.2), Depression (4.3.4), Psychoses and schizophrenia (4.3.6), Movement disorders (4.4), Nausea and labyrinth disorders (4.5), Pain (4.6), Thyroid disorders (6.9),Bladder and urinary disorders (7.1), Hormone responsive malignancy (8.4), Anaemias (9.1), Neutropenia (9.3.1), Platelet disorders (9.4), Hyperuricaemia and gout (10.2), Pain and inflammation in musculoskeletal disorders (10.4).[27] We will look up to 1 years prior to diagnosis.

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Initial data processing: Data will be assessed using data visualisation, outlier detection and quantifying missing values.

Analysis using unsupervised ML:

Step 1

Association rule mining is a rule-based ML method for 'interesting relationships' between variables for cases and controls. Association rules using a priori algorithm will be used to identify individual and combinations of medicines associated with BP.[14,15] A threshold of support and confidence will be decided from looking at patterns in the data and using clinical judgement to indicate the medicines which are commonly prescribed prior to BP. Support and confidence are measures of strength of association used in association rule learning. At the end we will have a list of individual and combinations of medicines associated with BP.

Step 2

We will characterise the data by undertaking a non-discriminatory approach. We will look at cases and controls separately to understand relationships between patient groups and BP. Controls will be used for moderation. We will employ clustering analysis to describe patient demographic and co-morbidity characteristics. Class imbalance handling techniques will be used as there will be more controls than cases in our dataset. ML will collapse patients into categories in a clinically meaningful way where numbers are small. At the end we will identify groups of patients with particular combinations of characteristics, associated with BP.

Step 3

We will determine how the groups in step 2 are associated with the rules identified in Step 1.

Ethical Approval

This study does not raise any ethical issues. Data in the CPRD are anonymised and provided to the researchers by the Medicines and Healthcare Regulatory Authority after external peer review and approval by their Independent Scientific Advisory Committee.

DISCUSSION

In this study we will look to see which medicines/vaccines are associated with BP, in general. We will provide updated and reliable estimates of risk of BP for drugs/vaccines commonly prescribed to older people. This study will (i) provide greater awareness of the risk of drug-associated BP amongst specialist and non-specialist healthcare professionals and therefore may facilitate earlier diagnosis of BP; (ii) support withdrawal of suspect medicines and switching to alternatives, where available, to achieve earlier remission of BP.

We will not be looking at drug recency, dosage and duration. If further funding is obtained, our research group plan to conduct a cohort design using a more granular approach (drug recency, dosage and duration) focussing on the therapeutic groups identified as the main risk factors in this study to provide further detailed information. Therefore, this project will be the important and essential start of work in the pharmaco-epidemiology of BP using electronic healthcare records. In this study, we will also not be able to investigate confounding by indication for dementia as the majority of people on antidementia medication will have dementia. We will interpret the results in light of this limitation. STROBE guidelines will be used when reporting the results.[28]

FUNDING

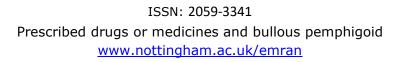## ACKOWLEDGEMENT AND DISCLAIMER

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