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Association between drugs and vaccines commonly prescribed to older people and bullous pemphigoid: a case–control study

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Abstract

Background Bullous pemphigoid (BP) is an autoimmune skin disease that mainly affects older people. Based on case series and small hospital-based studies, a number of drugs have been associated with BP. More reliable and precise estimates of associations between a broad selection of drugs/vaccines and BP will enable greater awareness of any potential increased risk of BP following the administration of certain medicines and help identify clinical, histological and genomic characteristics of drug-induced BP for different culprit drugs. Greater awareness could lead to earlier recognition or suspicion of BP and referral to a dermatologist for diagnosis. Earlier diagnosis may lead to less aggressive treatment and improved wellbeing.

Objectives To determine the association between drugs/vaccines commonly prescribed to older people and the risk of developing BP.

Methods We conducted a population-based nested case–control study between 1998 and 2021 using electronic primary care records from the Clinical Practice Research Datalink. We matched patients with BP with up to five controls. Exposures were drugs/vaccines commonly prescribed to older people. We used multivariable conditional logistic regression adjusting for multiple drug use. For antibiotics, in a sensitivity analysis, we considered that drugs may be prescribed for undiagnosed symptoms of BP that resemble skin infection (protopathic bias).

Results Antibiotics were associated with the highest risk of BP [odds ratio (OR) 4.60, 95% confidence interval (CI) 4.40–4.80]. However, after adjusting for protopathic bias, the OR decreased to 2.08 (95% CI 1.99–2.17). Also, after adjusting for protopathic bias, of all the antibiotic classes and subclasses, penicillins [OR 3.44, 95% CI 3.29–3.60 (sensitivity analysis OR 1.74, 95% CI 1.66–1.84)] and penicillinase-resistant penicillins [OR 7.56, 95% CI 7.15–8.00 (sensitivity analysis OR 2.64, 95% CI 2.45–2.85)] had the strongest associations with BP risk. Other drugs strongly associated with increased risk were gliptins (OR 2.77, 95% CI 2.37–3.23) and second-generation antipsychotics (OR 2.58, 95% CI 2.20–3.03).

Conclusions Healthcare professionals need to be aware of BP risk in older people, particularly when prescribing penicillinase-resistant penicillins, gliptins and second-generation antipsychotic drugs, to recognize and manage BP early. Owing to the low disease prevalence, we do not suggest avoiding certain drugs/vaccines to prevent BP. Further research should consider recency, dosage and duration of antibiotic treatments.

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Lay summary

Bullous pemphigoid (or 'BP' for short) is a serious and rare skin condition. It mainly affects older people. About 8 in every 100,000 people in the UK will develop BP for the first time each year. The initial symptoms are often very itchy skin and a red rash that can develop into painful blisters and open sores. Although we do not know which factors trigger BP, it has been suggested that certain medications may cause it. However, these findings have mainly been from small studies and specialist hospitals. It is important to provide reliable estimates of the risk of BP following medication use from a population that is representative of the whole of the UK.

This study was carried out in the UK, and may help GPs to suspect BP early on. This may allow them to refer patients to a dermatologist who will diagnose and treat symptoms. We used routinely collected data from more than 2,000 GP surgeries in the UK to find out the risk of BP. We also took into consideration that older people can take many medications at the same time. We found that some antibiotic, anti-diabetic and anti-psychotic drugs are associated with an increased risk of BP.

Our findings highlight how important it is to look for skin reactions after using certain medications, and to recognize and manage BP quickly. We advise against avoiding these medications, as most people taking them do not develop BP. Future research could explore how the dosage, treatment duration and recency of antibiotics affect the risk of BP.

What is already known about this topic?

- Bullous pemphigoid (BP) is predominantly a disease of older people.
- Numerous drugs have been reported to be associated with BP.
- The majority of previous findings are from case series or small hospital-based studies.

What does this study add?

- Reliable and precise estimates of the association between BP and several therapeutic groups, drug classes, subclasses and substances based on a large UK population-based study of over 16 800 people with BP.
- The need to raise awareness among healthcare professionals of increased BP risk following the use of certain drugs, including penicillins, penicillinase-resistant penicillins (flucloxacillin), gliptins and second-generation antipsychotics (olanzapine).

Bullous pemphigoid (BP), characterized by pruritus and blisters, is the most common autoimmune blistering skin disease.[1–3] BP is a rare disease, predominant in older people (prevalence 141 per 100 000 people older than 60 years of age).[3] BP can take years to resolve and has a threefold increased mortality risk than that of the general population.[2,3] BP is typically treated with oral prednisolone,[4,5] which has known side-effects, including osteoporosis and diabetes.[4,5] Despite being associated with high morbidity, mortality and healthcare costs,[6,7] the aetiology of BP is unknown.[2,3,8]

The pathogenesis of BP may be immune-mediated.[9] The pathomechanism starts with the binding of autoantibodies to hemidesmosome proteins BP180 and BP230 and ends with the release of enzymes inducing cell-matrix adhesion loss and the creation of subepidermal blisters.[10] Previously reported BP triggers include drugs, vaccines, neurological conditions (e.g. dementia) and genetic predisposition.[1,11–15] Previous studies have described drug-induced BP,[9,11,16,17] with the withdrawal of the culprit drug leading to remission.[18] Unlike idiopathic BP, drug-induced BP has diverse clinical characteristics, varying between culprit drugs,[11] making it difficult to diagnose and initiate earlier treatment.[11,19,20] Systematic reviews and case–control studies have reported various drugs to be associated with BP, including gliptins, anticholinergics, aldosterone antagonists, antibiotics and loop diuretics.[9,11,16,17,21] Most of the current evidence relies on case series or small hospital-based studies (likely to reflect severe presentations of BP).

Reliable and precise information on drugs/vaccines associated with BP risk is important in helping with earlier recognition in primary care and referral to a dermatologist for diagnosis. Earlier diagnosis may mean less severe, more manageable symptoms and less aggressive treatment. Furthermore, associations for a broad selection of drugs could help clinicians and researchers to identify clinical, histological and genomic characteristics of drug-induced BP, improve its recognition, understand its trigger mechanisms and compare differences between culprit drugs. To address this important knowledge gap, we conducted a large population-based nested case–control study using routinely collected electronic primary care records in the UK. The study design has allowed us to identify cases of BP, a rare disease, and account for multiple drug prescriptions (reflecting age-dependent polypharmacy).[22] Using electronic healthcare records from the Clinical Practice Research Datalink (CPRD; https://cprd.com/introduction-cprd), we matched patients with controls from the population without BP and conducted a study representative of the UK population.[23] We aimed to examine whether drugs and vaccines prescribed for common conditions in older people are associated with increased BP risk at the population level, accounting for other drug use. Our objective comprised obtaining more reliable and precise estimates for previously drugs/vaccines previously associated with BP and drugs that have not yet been investigated.

Patients and methods

Study design

We used a nested case–control study, a recommended design for rare diseases like BP and when multiple exposures are to be evaluated.[24,25] This study followed the RECORD-PE reporting guidelines.[26] We have previously published the protocol containing the full details of this study.[27]

Data source

The CPRD was used to find patients and controls for our study. The CPRD is a longitudinal database that contains anonymised, routinely collected healthcare records from more than 2000 general practices, comprising 60 million patients, 18 million currently registered at a practice, representing 26% of the UK population.[28,29] The data are from Vision and EMIS general practice systems, stored in GOLD and Aurum datasets.[23,30] These datasets cover UK and English-only practices, respectively.[23,30]

Cases and controls selection

We identified incident cases of BP (patients aged ≥18 years) between 1 January 1998 and 22 December 2021 using read codes from the patients' electronic clinical records (Appendix S1; see Supporting Information). We cannot specify exactly how the diagnoses were made, but we assumed that – for most patients – general practitioners (GPs) received confirmation from dermatologists who would have diagnosed BP from a skin biopsy and/or direct or indirect immunofluorescence. The GP would then add a BP read code to the patient's electronic records. Our previous validation study using inpatient data (Hospital Episode Statistics), identified BP codes with high positive predictive value (> 85%).[31] The index date was the earliest assigned BP code. At least 1 year of follow-up was required, to minimize the inclusion of prevalent cases.[32,33]

We matched up to five controls (without a diagnosis of BP at the index date) by birth year, sex and GP practice, using incidence density sampling.[34] We matched by GP practice to account for differences in diagnosis recording and prescribing.[33] Controls were registered at least 1 year before the index date of their matched patient. This step ensured controls had records in the same observation period and – if they later developed BP – no retrospective BP record was added after their registration. We verified whether we had sufficient patients with BP for our analysis by comparing the number of patients with BP with the power calculation described in Appendix S2 (see Supporting Information).[27]

Exposures

We selected drugs used commonly by older people.[35] We included latest prescriptions of antibiotics, antidiabetics, antihypertensive drugs, antithrombotic drugs, lipid-modifying drugs, analgesics, antidementia drugs, antiepileptic drugs, antipsychotic drugs and antidepressant drugs issued within 1 year before the index date. We included the latest influenza vaccine immunizations within 3 months before the index date. The cutoff points were based on previously reported durations of immune responses to drugs and vaccines.[11,36,37] The drugs were divided into therapeutic groups, defining the pathology they treat. Each group contained drug classes that describe their mode or mechanism of action. When applicable, a class comprised subclasses from the British National Formulary.[38] Clinicians (R.H.H., R.D.K.) helped develop product lists for all groups.

Confounding variables

We tested dementia, stroke, Parkinson disease (PD), Index of Multiple Deprivation (IMD) and ethnicity as confounders. All but IMD are potential risk factors for BP.[39–44] If the adjusted odds ratio (OR) changed by > 10% compared with the unadjusted OR, the condition was considered to be a confounder and included in the multivariable models. We classified people with dementia, stroke or PD if they had a clinical diagnosis at least 1 year before BP.

Statistical analysis

We used unadjusted, partially adjusted and multivariable conditional logistic regression models to determine the association between drugs and BP risk. Partially adjusted models checked whether drug groups were confounded by stroke, dementia or PD (Table S1; see Supporting Information).[39,40,42–44] Multivariable models were then developed to account for (i) therapeutic groups, (ii) classes and (iii) subclasses of drugs (with classes that could not be subdivided).

We conducted analyses separately for GOLD and Aurum, and then combined the datasets, adjusting for data source, if the results were similar. We used Bonferroni correction to adjust for multiple testing and considered a *P*-value < 0 .001 to be statistically significant and an OR > 2 to indicate a strong association.[45,46]

For ethnicity, we conducted multiple imputation using sex, age at diagnosis, deprivation and BP status. Data management and analyses were conducted in R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analyses

For antibiotics, we investigated protopathic bias potentially arising from treating symptoms of undiagnosed BP.[47] This analysis excluded 6 months of antibiotics prescriptions before the index date based on a mean diagnostic delay for BP.[36,48] We adjusted for the number of consultations (categorical variable) 6 months before the index date, to account for health-seeking behaviour (Appendix S3; see Supporting Information). To adjust for a possible increase in GP visits for people with BP (surveillance bias), we excluded people with any drug prescription within 3 months before BP.

Other sensitivity analyses explored biases, such as accounting for ethnicity and IMD (data from Hospital Episode Statistics-linked practices only), diagnostic delay by extending the exposure window, preceding skin infection diagnosis as BP can be misdiagnosed as such and a higher comorbidity burden in patients with BP by adjusting for Cambridge Multimorbidity Score comorbidities (Appendices S4, S5; see Supporting Information).[49]

Table 1 Study population characteristics ($n=96\,337$)

	Patients with BP ($n=16\,844$)	Controls without BP ($n=79\,493$)
Age at index date (years), mean (SD)	76.6 (14.1)	76.0 (14.1)
Age group (years)		
< 60	1868 (11.1)	9183 (11.6)
60–69	1876 (11.1)	9223 (11.6)
70–79	4510 (26.8)	22 039 (27.7)
80–89	6301 (37.4)	29 871 (37.6)
≥ 90	2289 (13.6)	9177 (11.5)
Sex		
Female	9350 (55.5)	44 363 (55.8)
Male	7494 (44.5)	35 130 (44.2)
Ethnicity[a]		
Asian	498 (3.0)	1336 (1.7)
Black	234 (1.4)	775 (1.0)
White	12 641 (75.0)	55 667 (70.0)
Other	155 (0.9)	624 (0.8)
Unknown	3316 (19.7)	21 091 (26.5)
Index of Multiple Deprivation		
1 (most affluent)	3100 (18.4)	14 997 (18.9)
2	2908 (17.3)	13 797 (17.4)
3	2897 (17.2)	13 147 (16.5)
4	2465 (14.6)	11 455 (14.4)
5 (most deprived)	2143 (12.7)	9694 (12.2)
Unknown	3331 (19.8)	16 403 (20.6)
Comorbidities diagnosed at least 1 year before the index date		
Dementia	1502 (8.9)	2679 (3.4)
Stroke	2675 (15.9)	8358 (10.5)
Parkinson disease	416 (2.5)	850 (1.1)

BP, bullous pemphigoid. [a]Modified ethnicity groups based on the Clinical Practice Research Datalink (CPRD) Aurum/GOLD higher-level classification derived from the official 2011 UK Census ethnicity categories.[68] The 'mixed' group (encompassing 'White and Black Caribbean', 'White and Black African', 'White and Asian' and 'Any other mixed background' ethnicities) was merged with the 'other' group (ethnicities in the 'other' group are not further specified in CPRD).

Additional analysis

For classes and subclasses associated with BP, we identified the top five most prescribed drug substances with an OR > 2 for risk of BP.

Results

Results for GOLD and Aurum were similar (Tables S2, S3; see Supporting Information). Therefore, we report results from the datasets combined.

Study population

The study population comprised 16 844 patients with BP and 79 493 controls (Figure S1; see Supporting Information). Table 1 presents the characteristics of the patients and controls. Median participant age was 80 years (interquartile range 71–86) (Table 1). Most patients with BP were female (55.5%) and White (75.1%). Dementia, stroke and PD were 2–3 times more prevalent in patients with BP than in controls.

Main analysis

More patients with BP were exposed to each drug/vaccine than controls [Figure 1; Table S4 (see Supporting Information)]. Stroke was not a confounder for any drug. Dementia was a confounder for mirtazapine, and PD was a confounder for monoamine oxidase inhibitors (Table S4). Both were accounted for in the multivariable analysis.

Antibiotics

Antibiotic exposure was associated with increased risk of BP [OR 4.60, 95% confidence interval (CI) 4.40–4.80]. Penicillinase-resistant penicillins were associated with the highest risk of BP (OR 7.56, 95% CI 7.15–8.00).

Antidiabetic drugs and insulins

Antidiabetic drugs and insulins were associated with an increased risk of BP (OR 1.35, 95% CI 1.26–1.44). Gliptins were the only class found to have a significant association with an increased risk of BP (OR 2.77, 95% CI 2.37–3.23; $P<0.001$).

Antihypertensive drugs

Antihypertensive drugs were associated with an increased risk of BP (OR 1.48, 95% CI 1.41–1.56). The highest OR for antihypertensive drug classes was reported for diuretics (OR 1.42, 95% CI 1.35–1.49). Thiazides and related diuretics (OR 1.36, 95% CI 1.28–1.44) and loop diuretics (OR 1.32, 95% CI 1.24–1.41) were the only diuretic subclasses associated with an increased risk of BP.

Antithrombotic drugs

Antithrombotic drugs were associated with an increased risk of BP (OR 1.33, 95% CI 1.26–1.39); the only class with a

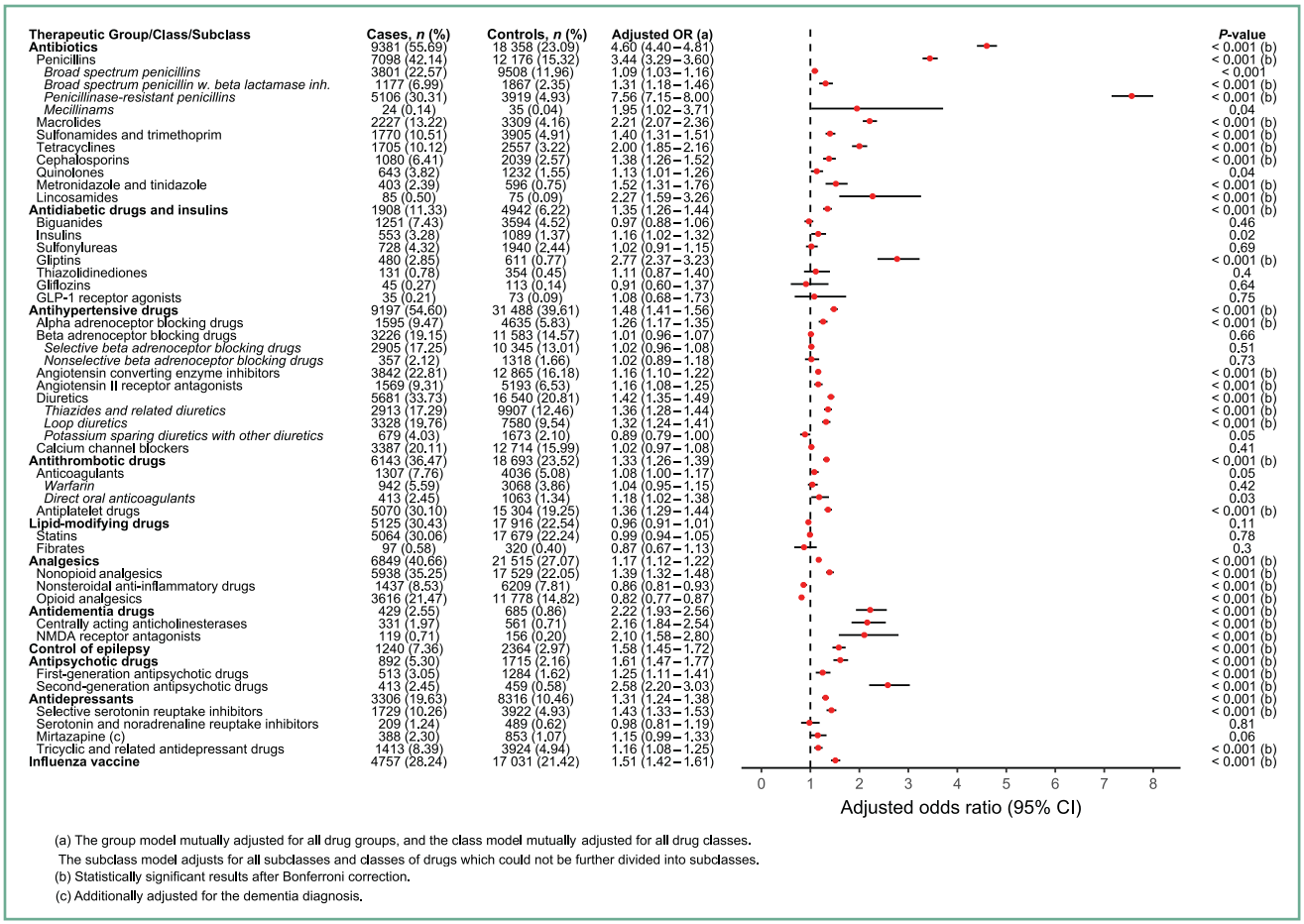

Figure 1 Estimates of bullous pemphigoid (BP) risk [odds ratio (OR)] following the latest drug prescriptions issued within 1 year before BP diagnosis, accounting for multiple drug exposures, using combined GOLD and Aurum datasets. CI, confidence interval; GLP-1, glucagon-like peptide-1; NMDA, *N*-methyl-D-aspartate.

significant association was antiplatelet drugs (OR 1.36, 95% CI 1.29–1.44; $P<0.001$).

Lipid-modifying drugs

Lipid-modifying drugs were not found to be associated with BP.

Analgesics

Analgesics were associated with an increased risk of BP (OR 1.17, 95% CI 1.12–1.22), likely attributed to the class of nonopioid analgesics (OR 1.39, 95% CI 1.32–1.48). Two classes of analgesics were associated with a reduced risk of BP: nonsteroidal anti-inflammatory drugs (OR 0.86, 95% CI 0.81–0.93) and opioids (OR 0.82, 95% CI 0.77–0.87).

Antidementia drugs

Antidementia drugs were associated with an increased risk of BP (OR 2.22, 95% CI 1.93–2.56), including specific classes such as centrally-acting anticholinesterases (OR 2.16, 95% CI 1.84–2.54) and *N*-methyl-D-aspartate (NMDA) receptor antagonists (OR 2.10, 95% CI 1.58–2.80).

Antiepileptic drugs

Antiepileptic drugs were associated with an increased risk of BP (OR 1.58, 95% CI 1.45–1.72).

Antipsychotic drugs

Antipsychotic drugs were associated with an increased risk of BP (OR 1.61, 95% CI 1.47–1.77). Second-generation antipsychotic drugs had the strongest association with BP (OR 2.58, 95% CI 2.20–3.03).

Antidepressant drugs

Antidepressant drugs were associated with an increased risk of BP (OR 1.31, 95% CI 1.24–1.38). Drug classes associated with BP were selective serotonin reuptake inhibitors (OR 1.43, 95% CI 1.33–1.53) and tricyclic antidepressants (OR 1.16, 95% CI 1.08–1.25).

Influenza vaccine

Influenza vaccine was associated with an increased risk of BP (OR 1.51, 95% CI 1.42–1.61). For univariate and partially adjusted results, see Table S4.

Sensitivity analyses

Protopathic bias

After excluding antibiotic prescriptions 6 months before a diagnosis of BP, the OR for antibiotics changed from 4.60 to 2.08 (Figure 2). The OR for penicillins also dropped (from 3.44 to 1.74), with the highest reduction reported for penicillinase-resistant penicillins (from 7.56 to 2.64). Table S5

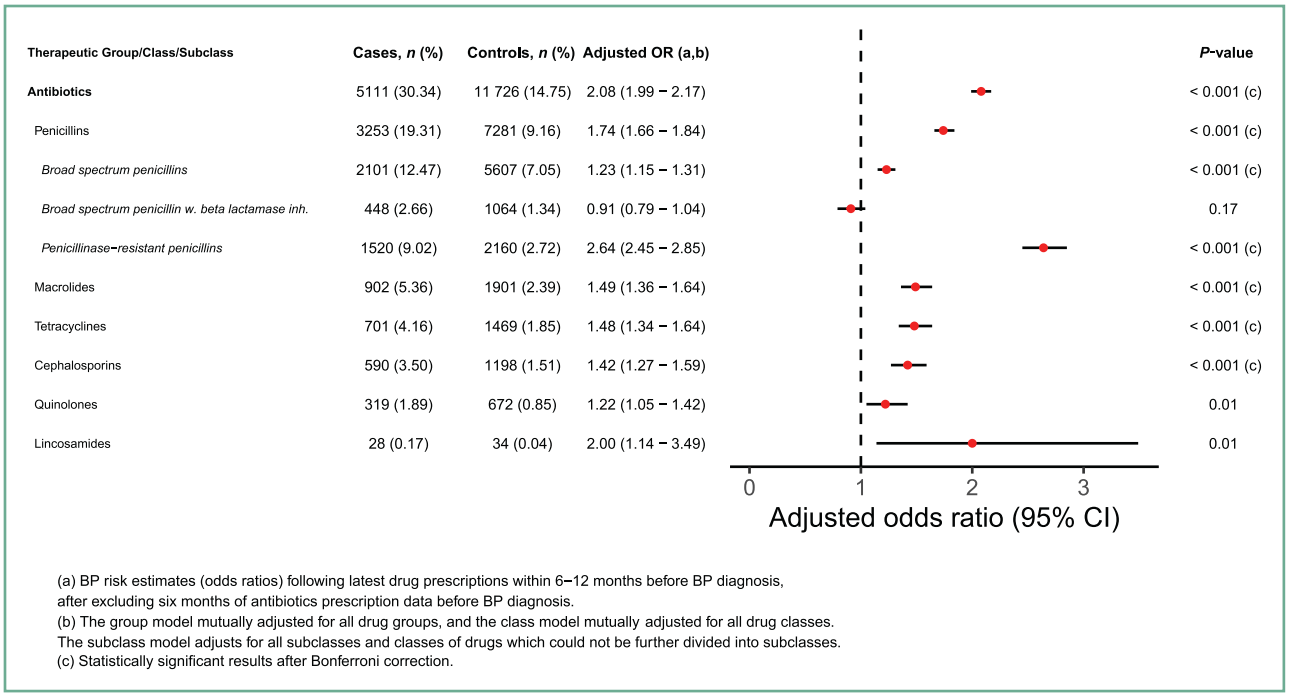

Figure 2 Estimates of bullous pemphigoid (BP) risk [odds ratio (OR)] following latest drug prescriptions within 6–12 months before BP diagnosis after excluding 6 months of antibiotics prescription before BP diagnosis and accounting for multiple drug exposures, using combined GOLD and Aurum datasets. CI, confidence interval.

shows all results for this sensitivity analysis (see Supporting Information).

After adjusting for the impact of the number of consultations, antibiotics remained the group most strongly associated with BP (OR 3.63, 95% CI 3.47–3.79). Penicillins (OR 2.86, 95% CI 2.73–2.99) and penicillinase-resistant penicillins remained associated with an increased risk of BP (OR 6.57, 95% CI 6.20–6.95). Nearly all other drugs had lower ORs than in the main analysis. Almost 86% of patients with BP attended at least one consultation in the 6 months before they were diagnosed with BP vs. 59% of controls (Table S6; see Supporting Information).

Surveillance bias

After excluding patients with drug prescriptions in the 3 months before a diagnosis of BP, antibiotics remained strongly associated with BP (OR 3.46, 95% CI 2.94–4.08). Penicillins (OR 3.26, 95% CI 2.69–3.95) and the penicillinase-resistant subclass were also associated with an increased risk of BP (OR 4.71, 95% CI 3.50–6.33). The influenza vaccine was no longer associated with BP (Table S7; see Supporting Information).

Appendix S6 (see Supporting Information) contains the results of other sensitivity analyses, including the effect of ethnicity and IMD (Table S8; see Supporting Information), a longer exposure window (Table S9; see Supporting Information), a preceding skin infection diagnosis (Table S10; see Supporting Information) and comorbidity burden (Table S11; see Supporting Information).

Additional analysis

Flucloxacillin had the highest adjusted OR [OR 7.74, 95% CI 7.31–8.19 (adjusted for protopathic bias: OR 3.10, 95% CI 2.68–3.59); Figure 3] followed by linagliptin (OR 5.05, 95% CI 3.99–6.40). Other strong associations with BP were estimated for second-generation antipsychotics risperidone (OR 2.63, 95% CI 2.04–3.38), olanzapine (OR 2.26, 95% CI 1.64–3.12) and the antidementia drug memantine (OR 2.30, 95% CI 1.70–3.12). See Table S12 for the complete results (see Supporting Information).

Discussion

This large population-based study has shown that several therapeutic groups, classes, subclasses and substances are associated with the risk of BP, after adjusting for multiple drug use. Antibiotics were associated with a high risk of BP, particularly flucloxacillin, with more than a twofold increase in BP risk following protopathic bias analysis. Gliptins were the only antidiabetic drug associated with an increased risk of BP (3-fold increase), and linagliptin had the strongest association (fivefold increase). We also estimated an increased risk of BP following antidementia drugs, particularly centrally acting anticholinesterases and NMDA receptor antagonists. Furthermore, we report the first ever estimates of BP risk following a second-generation antipsychotic drug (olanzapine; 2.3-fold increased risk) and the influenza vaccine (1.5-fold increased risk). The latter did not stay statistically significant after accounting for surveillance bias.

We compared our findings with previous studies that investigated the associations between drugs and BP (Table S13; see Supporting Information). To our knowledge, we have conducted the largest population-based case–control study to date (> 16 000 cases of BP).

Our results were similar to those of Verheyden *et al.*, who reported strong associations with gliptins, loop diuretics,

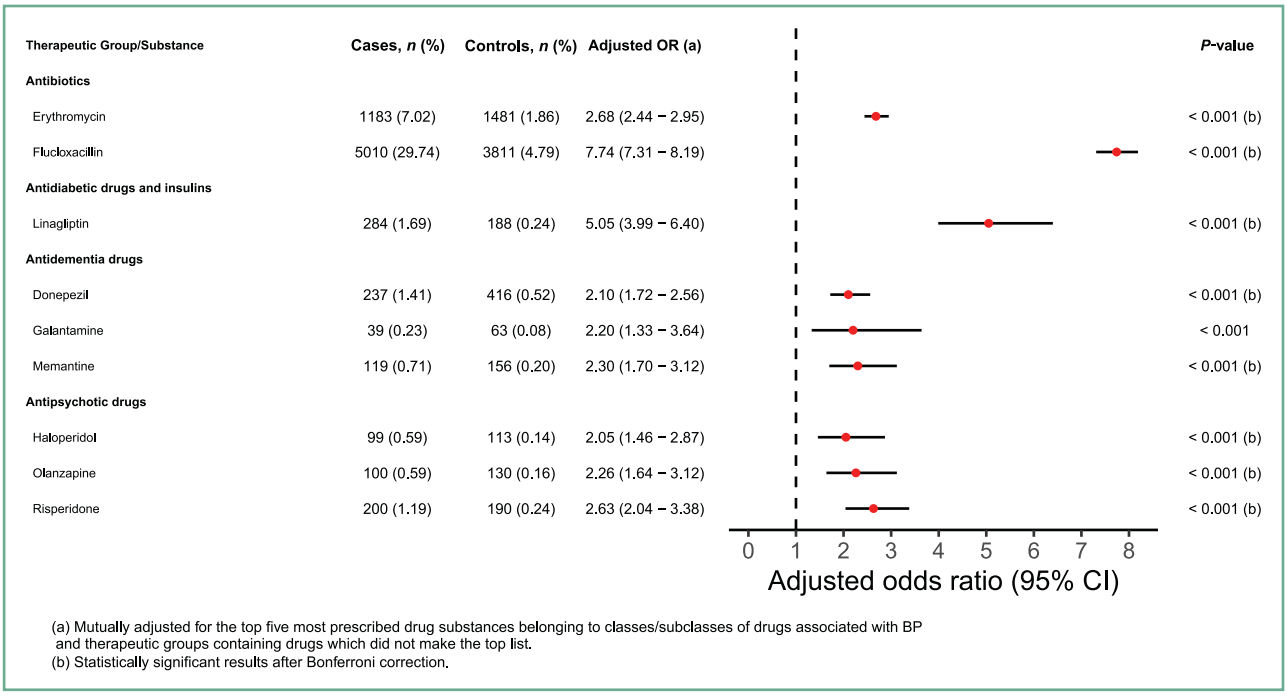

Figure 3 Estimates of bullous pemphigoid (BP) risk [odds ratio (OR)] of drug substances following latest prescriptions issued within 1 year before BP diagnosis accounting for multiple drug exposures, using combined GOLD and Aurum datasets. CI, confidence interval.

penicillins and thiazides.[11] Regarding drugs prescribed for neurological disorders, our results confirmed the association between fluoxetine (Table S12), risperidone (Table S12) and BP reported by Verheyden *et al.*[11] However, unlike their systematic review, we found no association between galantamine, gabapentin and BP (Table S12).[11] Furthermore, we have reported results for olanzapine, a second-generation antipsychotic drug, which has not been previously investigated.

Compared with our study, the meta-analysis of Liu *et al.* found an increased risk of BP following gliptins (pooled OR 1.92, 95% CI 1.55–2.38).[16] Our estimate (OR 2.77, 95% CI 2.3–3.23) was based on fewer cases, but the studies included in the meta-analysis were mostly hospital-based.[16] Our estimate regarding gliptins was also confirmed by a large CPRD cohort study by Douros *et al.* (adjusted hazard ratio 2.21, 95% CI 1.45–3.38).[50]

In a UK-based single-hospital case–control study by Lloyd-Lavery *et al.*,[17] loop diuretics (OR 3.8, 95% CI 1.5–9.7) and antibiotics (OR 3.4, 95% CI 1.1–11.2) were associated with a high risk of BP, but with higher estimates than ours [OR 1.32 (95% CI 1.24–1.41) and OR 2.08 (95% CI 1.99–2.17), respectively].[17] These differences may be attributed to different settings and not adjusting for multiple drug use. Furthermore, we adjusted for protopathic bias in antibiotic prescribing, which the other authors did not address.

The increased risk of BP following penicillins could be related to metabolism, which exposes a thiol group possibly involved in the drug reaction pathogenesis.[9] After diagnosing BP, clinicians may need to avoid prescribing penicillins, particularly the penicillinase-resistant subclass. Gliptin treatment, while having an overall lower risk of hypoglycaemia than other antidiabetic drugs,[51] may also need to be altered if a person develops BP, to prevent prolonged disease progression. However, owing to the low absolute number of patients who develop BP vs. the number of people who are treated with these drugs and do not develop BP, we do not suggest avoiding drugs with reported associations with BP. Instead, early biopsy and direct immunofluorescence should be performed in cases of acute pruritus onset and skin changes, to determine if a patient has BP and then drug-induced factors should be evaluated.

Previous studies have reported the time to BP onset after drug exposure as being between 24 hours and 16.5 months.[11,52–55] Therefore, prompt withdrawal of the offending agent and the initiation of treatment for BP before symptoms become severe may be required.

The combined CPRD GOLD and Aurum datasets represent > 2000 UK GP practices.[23] These features allowed for a study design with sufficient power and generalizable results. The detailed electronic prescriptions from the CPRD allowed us to account for multiple exposures to many groups of drugs. We explored various biases by sensitivity analyses. The study's main limitation was possible confounding by indication. The estimates for antidementia drugs were probably affected by this bias as dementia has previously been associated with BP.[13,56–59] Therefore, we cannot infer whether the association was between antidementia drugs or dementia per se and BP. Schizophrenia, bipolar disorder, epilepsy and stroke have also been reported to be associated with BP.[14,43,56–64] We therefore advise cautious interpretation of the associations between the drugs indicated for these conditions and BP. Owing to the nature of routinely collected data, unmeasured confounding may have also affected our results. Patients with BP have poorer outcomes than people without BP, as evidenced by a higher 2-year mortality rate.[3] Our comorbidity data also indicated that 51% of patients with BP had at least one comorbidity vs. only 39% of controls (Table S14; see Supporting Information), which could

explain why some drugs were associated with BP. Hence, we cannot always imply a drug-induced mechanism. We tried to minimize unmeasured confounding by conducting sensitivity analyses, such as adjusting for comorbidity, health-seeking behaviour and skin infection before diagnosis, which gave similar results to the main analysis.

Public health policies, like free influenza immunization for people aged > 65 years or with long-term conditions,[65] could also increase vaccine exposure in sicker patient populations such as those with BP. Our surveillance bias analysis supported this interpretation, as it reported no association between the influenza vaccine and BP. Given an OR < 2, and that BP is generally rare, we argue that the benefits of influenza vaccines outweigh the low risk of BP in the general population.

Some drugs were licensed after our study started in 1998, which may explain the small number of patients with BP and controls exposed to said drugs. For example, linagliptin was approved in the UK in 2011,[66,67] which meant there were no prescription data for this drug for 13 years of our study. Finally, the risk of BP after antibiotic treatment could have been overestimated in our analysis, but a strong association remained after adjusting for protopathic bias and skin infections.

Clinicians need to be aware of the risk of BP in older people following administration of penicillinase-resistant penicillins, gliptins and second-generation antipsychotic drugs to recognize BP early and consider withdrawal or administration of alternative drugs that have a lower risk of causing BP. We do not suggest avoiding drugs/vaccines with the reported associations, as most people use them without developing BP and the absolute number of patients with BP is low. Further research should consider recency, dosage and duration of antibiotic treatments, and whether neurological conditions or drugs indicated for them are associated with BP.

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Conflicts of interest

During the course of this work V.P. received salary funding via King's College London from the National Institute for Health and Care Research's (NIHR) academic clinical lecturer scheme, University of Nottingham as Associate Professor, via the NIHR East Midlands scholarship scheme (hosted by NHS Nottingham and Nottinghamshire and the University of Nottingham) and via University of Nottingham as Clinical Associate Professor via the NIHR Senior Clinical and Practitioner Research Award. V.P. reports associations with King's College London and the University of Nottingham. The other authors declare no conflicts of interest.

Data availability

Clinical Practice Research Datalink (CPRD) provided the data supporting this study's findings under a licence that does not permit sharing. The data are available by applying to CPRD directly via www.cprd.com.

Ethics statement

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

Patient consent

Not applicable.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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