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Research letter:

Drugs used for neurological and psychiatric conditions increase the risk of bullous pemphigoid: a case-control study

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To the editor: The association between neurological diseases and bullous pemphigoid (BP) is well established[1]. However, it has not yet been established whether drugs that affect the nervous system can influence the onset of BP. The aim of this study was to determine whether patients who had received drugs used to treat neurological and psychiatric diseases had an altered risk for BP.

We searched the Finnish Care Register for Health Care database for all patients who received a diagnosis of BP between 1987 and 2013. The search returned data for 4524 patients and due the drug reimbursement data the present analysis used data from the 3397 who were diagnosed between 1997 and 2013. A total of 66138 basal cell carcinoma (BCC) patients were identified and 12941 of these were randomly selected to be matched to the BP population by age, sex and year of diagnosis in a 4:1 ratio. Characteristics of study populations are shown in Table I.

The associations between the use of each drug for neurological and psychiatric diseases purchased in the previous two years and BP incidence were evaluated using a conditional logistic regression model and presented with odds ratios (ORs) and 95% confidence intervals. The associations that were statistically significant are shown in Table II. Those that particularly elevated the risk of BP include periciazine, melperone, haloperidol, biperiden and risperidone. At the drug class level, the butyrophenone derivates and the anti-dementia anticholinesterases were the only groups in which all constituent drugs were significantly associated with an increased risk for BP. Hydroxyzine seemed to associate with remarkable increase in the risk for BP, but this probably reflects use of hydroxyzine to treat pruritus that manifested as a pre-diagnosis BP symptom, rather than hydroxyzine pre-disposing patients to BP. The mean time interval between the first purchase of these drugs and diagnosis of BP was more than one year (data not shown), except for hydroxyzine (263 days).

The use of dipeptidyl peptidase-4 inhibitors (DPP-4i), especially vildagliptin, has recently been shown to markedly increase the risk of BP[2]. Certain neuroleptics, aldosterone antagonists and loop diuretics have also been reported to be risk factors for BP[3,4]. The present study demonstrates that the use of many of the selected neurological and psychiatric drugs is more common in BP patients than in controls and exposure to these medications increases the risk of BP. Since the ORs were adjusted for several psychiatric and neurological diagnoses that the studied drugs are used for, these findings cannot be explained solely by the appearance of

psychiatric and neurological conditions as BP comorbidities. As previously seen with DPP-4is, the time interval between first drug exposure and the diagnosis of BP was rather long[5]. However, considering their pharmacological properties and chemical structures of the drugs that were most strongly associated with BP, no definite similarities were apparent.

Our findings suggest that the use of drugs that affect the nervous system may contribute to the onset of BP, but additional studies are required to clarify this association.

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Table I. Characteristics of bullous pemphigoid cases and basal cell carcinoma controls.

	Cases n = 3397 (%)	**Controls n = 12941 (%)[1]**
Female	2028 (59.7)	7766 (60.0)
Male	1369 (40.3)	5175 (40.0)
Age (years), mean	76.6	76.7

[1] Age, sex and year of the diagnosis matched in 1:4 ratio. Due to availability of drug reimbursement data, 579 patients had fewer than intended 4 basal cell carcinoma controls

Table II. Proportions of bullous pemphigoid patients and controls exposed to drugs used for neurological and psychiatric conditions: significant associations.

Drug [1]	Group	total	N (%)	OR (95% CI)	Adjusted OR (95% CI)[2]
carbamazepine	cases	3397	90 (2.6)	2.26 (1.73 - 2.95)	1.57 (1.12 - 2.20)
	controls	12941	154 (1.2)	Reference	Reference
pregabalin	cases	3397	122 (3.6)	1.26 (1.02 - 1.55)	1.24 (1.00 - 1.53)
	controls	12941	383 (3.0)	Reference	Reference
biperiden	cases	3397	16 (0.5)	2.59 (1.37 - 4.92)	2.94 (1.42 – 6.09)
	controls	12941	24 (0.2)	Reference	Reference
levodopa and decarboxylase inhibitor	cases	3397	110 (3.2)	2.20 (1.74 - 2.79)	1.85 (1.10 - 3.12)
	controls	12941	196 (1.5)	Reference	Reference
levomepromazine	cases	3397	44 (1.3)	3.08 (2.06 - 4.61)	2.84 (1.81 - 4.48)
	controls	12941	54 (0.4)	Reference	Reference
perphenazine	cases	3397	34 (1.0)	2.23 (1.46 - 3.42)	1.82 (1.09 – 3.06)
	controls	12941	57 (0.4)	Reference	Reference
periciazine	cases	3397	15 (0.4)	4.79 (2.24 - 10.3)	7.55 (2.91 – 19.6)
	controls	12941	12 (0.1)	Reference	Reference
haloperidol	cases	3397	49 (1.4)	2.94 (2.01 - 4.30)	3.00 (1.93 - 4.65)
	controls	12941	63 (0.5)	Reference	Reference
melperone	cases	3397	41 (1.2)	3.50 (2.29 - 5.34)	4.00 (2.46 – 6.49)
	controls	12941	45 (0.3)	Reference	Reference
quetiapine	cases	3397	97 (2.9)	2.13 (1.66 - 2.75)	1.62 (1.20 - 2.18)
	controls	12941	178 (1.4)	Reference	Reference
sulpiride	cases	3397	13 (0.4)	2.56 (1.25 - 5.25)	2.37 (1.12 – 5.00)
	controls	12941	19 (0.1)	Reference	Reference
risperidone	cases	3397	172 (5.1)	3.06 (2.49 - 3.75)	3.04 (2.38 - 3.89)
	controls	12941	225 (1.7)	Reference	Reference
hydroxyzine	cases	3397	134 (3.9)	17.3 (11.5 - 26.0)	17.3 (11.5 – 26.0)
	controls	12941	37 (0.3)	Reference	Reference
diazepam	cases	3397	130 (3.8)	1.35 (1.10 - 1.66)	1.33 (1.08 - 1.63)
	controls	12941	372 (2.9)	Reference	Reference

chlordiazepoxide	cases	3397	18 (0.5)	2.16 (1.21 - 3.85)	2.15 (1.20 – 3.84)
	controls	12941	32 (0.2)	Reference	Reference
oxazepam	cases	3397	244 (7.2)	1.38 (1.19 - 1.61)	1.34 (1.15 - 1.56)
	controls	12941	688 (5.3)	Reference	Reference
lorazepam	cases	3397	73 (2.1)	1.58 (1.19 - 2.08)	1.48 (1.11 - 1.95)
	controls	12941	177 (1.4)	Reference	Reference
nitrazepam	cases	3397	38 (1.1)	1.84 (1.24 - 2.72)	1.84 (1.24 - 2.72)
	controls	12941	79 (0.6)	Reference	Reference
temazepam	cases	3397	326 (9.6)	1.36 (1.19 - 1.55)	1.35 (1.18 - 1.55)
	controls	12941	955 (7.4)	Reference	Reference
zopiclone	cases	3397	567 (16.7)	1.14 (1.03 - 1.27)	1.13 (1.02 - 1.26)
	controls	12941	1945 (15.0)	Reference	Reference
amitriptyline	cases	3397	75 (2.2)	1.62 (1.23 - 2.13)	1.60 (1.20 - 2.12)
	controls	12941	180 (1.4)	Reference	Reference
doxepin	cases	3397	60 (1.8)	2.26 (1.64 - 3.12)	2.33 (1.66 - 3.27)
	controls	12941	103 (0.8)	Reference	Reference
citalopram	cases	3397	317 (9.3)	1.87 (1.63 - 2.16)	1.83 (1.58 – 2.12)
	controls	12941	681 (5.3)	Reference	Reference
sertraline	cases	3397	43 (1.3)	1.73 (1.20 - 2.48)	1.68 (1.13 - 2.48)
	controls	12941	96 (0.7)	Reference	Reference
escitalopram	cases	3397	107 (3.1)	1.69 (1.34 - 2.14)	1.62 (1.26 – 2.09)
	controls	12941	249 (1.9)	Reference	Reference
mianserin	cases	3397	37 (1.1)	1.72 (1.16 - 2.54)	1.78 (1.15 - 2.74)
	controls	12941	82 (0.6)	Reference	Reference
mirtazapine	cases	3397	195 (5.7)	1.36 (1.15 - 1.61)	1.30 (1.09 - 1.56)
	controls	12941	559 (4.3)	Reference	Reference
venlafaxine	cases	3397	47 (1.4)	1.85 (1.30 - 2.63)	2.15 (1.41 – 3.27)
	controls	12941	98 (0.8)	Reference	Reference
duloxetine	cases	3397	28 (0.8)	1.86 (1.18 - 2.94)	1.81 (1.07 – 3.06)
	controls	12941	59 (0.5)	Reference	Reference

donepezil	cases	3397	111 (3.3)	2.03 (1.61 - 2.57)	1.40 (1.02 - 1.94)
	controls	12941	220 (1.7)	Reference	Reference
rivastigmine	cases	3397	87 (2.6)	2.46 (1.87 - 3.23)	2.11 (1.47 – 3.03)
	controls	12941	141 (1.1)	Reference	Reference
galantamine	cases	3397	48 (1.4)	2.38 (1.66 - 3.41)	1.75 (1.07 - 2.85)
	controls	12941	79 (0.6)	Reference	Reference
carbachol	cases	3397	8 (0.2)	2.74 (1.10 - 6.81)	2.82 (1.12 – 7.12)
	controls	12941	11 (0.1)	Reference	Reference
memantine	cases	3397	142 (4.2)	2.98 (2.38 - 3.73)	2.34 (1.67 – 3.26)
	controls	12941	200 (1.5)	Reference	Reference

[1] statistically significant results (defined by P <0.05) from analyses of all drugs from Anatomical Therapeutic Chemical-classification system main group N, Nervous system (excluding N01-N02).

[2] Adjusted for diagnoses of the following neurological and psychiatric conditions: Alzheimer's disease, vascular dementia, other/unspecified dementia, Parkinson's disease, multiple sclerosis, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, epilepsy, schizotypal and delusional disorder, schizophrenia, bipolar affective disorder, major depressive disorder, neurotic, stress-related and somatoform disorders, personality disorders, delirium due to known physiological condition, other mental disorders due to known physiological condition, personality and behavioral disorders due to known physiological condition, unspecified mental disorder due to known physiological condition.