

Data supplement to Huang et al. Use of lithium and cancer risk in patients with bipolar disorder: population-based cohort study. Br J Psychiatry doi: 10.1192/bjp.bp.116.181362

Table DS1 ICD-9-CM codes for comorbidity

Condition	ICD-9-CM code
Myocardial infarction	410, 412
Congestive heart failure	428
Other acute ischemic heart disease	411, 413
Other chronic ischemic heart disease	414.0, 414.2, 414.8, 414.9, 429.2
Peripheral vascular disease	443.9, 441, 785.4, V43.4, Procedure 38.48
Cerebrovascular disease	430-438
Dementia	290
Chronic pulmonary disease	490-496, 500-505, 506.4
Connective tissue disease	710.0-710.1, 710.4, 714.0-714.2, 714.81,725
Ulcer disease	531-534
Mild liver disease	571.2, 571.4-571.6
Diabetes	250
Hemiplegia or paraplegia	344.1, 342
Moderate or severe renal disease	582, 583-583.7, 595, 586, 588
Moderate or severe liver disease	456.0-456.2, 572.2-572.8
AIDS/HIV	042-044
Hypertension	401-405
Dyslipidemia	272
Schizophrenia	295
Other psychosis	290.8, 290.9, 297-299, 780.1
Depression	293.83, 296.2, 296.3, 296.9, 298.0, 300.4, 311
Anxiety disorders	300.0, 300.2, 300.3
Alcohol used disorders	291, 303, 305.0
Non-alcohol substance use disorders	292, 304, 305, except 305.0

Table DS2 ATC codes for study drugs

Category (ATC code)	Generic names (ATC code)
Lithium	Lithium carbonate, Lithium sulfate (N05AN01); defined daily dose: 24 mmol
Anticonvulsants	Carbamazepine (N03AF01), Oxcarbazepine (N03AF02), Valproate (N03AG01), Lamotrigine (N03AX09), Topiramate (N03AX11), Gabapentin (N03AX12)
First-generation antipsychotics	Chlorpromazine (N05AA01), Methotrimeprazine (N05AA02), Fluphenazine (N05AB02), Prochlorperazine (N05AB04), Trifluoperazine (N05AB06), Thioridazine (N05AC02), Pipotiazine (N05AC04), Haloperidol (N05AD01), Flupentixol (N05AF01), Pimozide (N05AG02), Penfluridol (N05AG03), Loxapine (N05AH01), Sulpiride (N05AL01), Amisulpride (N05AL05)
Second-generation antipsychotics	Ziprasidone (N05AE04), Clozapine (N05AH02), Olanzapine (N05AH03), Quetiapine (N05AH04), Risperidone (N05AX08), Aripiprazole (N05AX12), Zotepine (N05AX11), Paliperidone (N05AX13)
Serotonin-specific reuptake inhibitors	Fluoxetine (N06AB03), Citalopram (N06AB04), Paroxetine (N06AB05), Sertraline (N06AB06), Fluvoxamine (N06AB08), Escitalopram (N06AB10)
Tricyclic antidepressants	Imipramine (N06AA02), Clomipramine (N06AA04), Amitriptyline (N06AA09), Doxepin (N06AA12), Dothiepine (N06AA16), Maprotiline (N06AA21)
Anxiolytics/hypnotics	Diazepam (N05BA01), Chlordiazepoxide (N05BA02), Medazepam (N05BA03), Oxazepam (N05BA04), Clorazepate (N05BA05), Lorazepam (N05BA06), Bromazepam (N05BA08), Clobazam (N05BA09), Prazepam (N05BA11), Alprazolam (N05BA12), Nordazepam (N05BA16), Fludiazepam (N05BA17), Meprobamate (N05BC01), Buspirone (N05BE01), Amobarbital (N05CA02), Secobarbital (N05CA06), Flurazepam (N05CD01), Nitrazepam (N05CD02), Flunitrazepam (N05CD03), Estazolam (N05CD04), Triazolam (N05CD05), Lormetazepam (N05CD06), Temazepam (N05CD07), Midazolam (N05CD08), Brotizolam (N05CD09), Zopiclone (N05CF01), Zolpidem (N05CF02), Zaleplon (N05CF03)
Angiotensin-converting enzyme inhibitor	Captopril (C09AA01), Enalapril (C09AA02), Lisinopril (C09AA03), Perindopril (C09AA04), Ramipril (C09AA05), Quinapril (C09AA06), Benazepril (C09AA07), Cilazapril (C09AA08), Fosinopril (C09AA09), Imidapril (C09AA16)

Angiotensin II receptor blockers	Losartan (C09CA01), Eprosartan (C09CA02), Valsartan (C09CA03), Irbesartan (C09CA04), Candesartan (C09CA06), Telmisartan (C09CA07)
Statins	Simvastatin (C10AA01), Lovastatin (C10 AA02), Pravastatin (C10AA03), Fluvastatin (C10AA04), Atorvastatin(C10AA05), Rosuvastatin (C10AA07), Pitavastatin (C10AA08)
Metformin	Metformin (A10BA02)
Sulfonylureas	Glyburide (A10BB01), Chlorpropamide (A10BB02), Tolbutamide (A10BB03), Glibronuride (A10BB04), Tolamide(A10BB05), Glipizide (A10BB07), Gliquidone (A10BB08), Gliclazide (A10BB09), Glimepiride (A10BB12), Acetohexamide(A10BB31)
Systemic steroids	Betamethasone (H02AB01), Dexamethasone (H02AB02), Methylprednisolone (H02AB04), Prednisolone (H02AB06), Prednisone (H02AB07), Triamcinolone (H02AB08), Hydrocortisone (H02AB09), Cortisone (H02AB10)
Non-steroid anti-inflammatory drugs	Phenylbutazone (M01AA01), Indomethacin (M01AB01), Sulindac (M01AB02), Tolmetin (M01AB03), Diclofenac (M01AB05), Etodolac (M01AB08), Acemetacin (M01AB11), Ketorolac (M01AB15), Aceclofenac (M01AB16), Piroxicam (M01AC01), Tenoxicam (M01AC02), Meloxicam (M01AC06), Ibuprofen (M01AE01), Naproxen (M01AE02), Ketoprofen (M01AE03), Fenoprofen (M01AE04), Fenbufen (M01AE05), Flurbiprofen (M01AE09), Tiaprofenic acid (M01AE11), Mefenamic acid (M01AG01), Flufenamic acid (M01AG03), Nabumetone (M01AX01), Niflumic acid (M01AX02), Benzydamine (M01AX07), Nimesulide (M01AX17)
Aspirin	Aspirin (N02BA01)
COX-2 inhibitor	Celecoxib (M01AH01), Rofecoxib (M01AH02), Etoricoxib (M01AH05)

Table DS3 Site-specific cancer incidence and hazard ratios

Site (ICD-9 code)	Anticonvulsants only (n=3250)		Lithium ± anticonvulsants (n=1479)		HR ^b (95% CI)
	No. of cases (%)	Incidence rate (95% CI) ^a	No. of cases (%)	Incidence rate (95% CI) ^a	
Total (140-208)	86(2.65)	4.740 (4.319-5.201)	29(1.96)	2.664 (2.270-3.126)	0.735 (0.554-0.974)
Lip, oral cavity, and pharynx (140-149)	9 (0.28)	0.496 (0.444-0.555)	2 (0.14)	0.184 (0.145-0.233)	0.189 (0.062-0.573)
Lip, oral cavity, and pharynx (140-149, except 142 and 147)	7 (0.22)	0.386 (0.343-0.434)	2 (0.14)	0.184 (0.148-0.229)	
Respiratory system and intrathoracic organs (160-165)	9 (0.28)	0.496 (0.441-0.557)	3 (0.20)	0.276 (0.225-0.337)	0.490 (0.196-1.222)
Lung (162)	7 (0.22)	0.386 (0.343-0.434)	2 (0.14)	0.184 (0.148-0.229)	
Digestive organs and peritoneum (150-159)	38 (1.17)	2.094 (1.898-2.311)	10 (0.68)	0.918 (0.758-1.113)	0.751 (0.478-1.178)
Stomach (151)	0 (0.00)	-	1 (0.07)	0.092 (0.082-0.102)	
Colorectal (153-154)	12 (0.37)	0.661 (0.594-0.736)	2 (0.14)	0.184 (0.141-0.239)	
Liver (155)	20 (0.62)	1.102 (0.998-1.218)	3 (0.20)	0.276 (0.213-0.357)	
Bone, skin, and connective and other soft tissue (170-173)	2 (0.06)	0.110 (0.10-0.13)	2 (0.14)	0.184 (0.158-0.213)	3.012 (0.798-11.365)
Breast, female only (174)	7 (0.22)	0.386 (0.339-0.438)	4 (0.27)	0.367 (0.310-0.435)	0.696 (0.293-1.653)
Genitourinary (179-189)	13 (0.40)	0.716 (0.638-0.805)	5 (0.34)	0.459 (0.381-0.554)	1.014 (0.472-2.179)
Prostate (185)	6 (0.18)	0.331 (0.297-0.368)	0 (0.00)	-	
Cervix uteri, body of uterus (179-180,182)	2 (0.06)	0.110 (0.093-0.131)	3 (0.20)	0.276 (0.239-0.317)	
Bladder (188)	1 (0.03)	0.055 (0.047-0.065)	1 (0.07)	0.092 (0.078-0.108)	
Kidney (189)	2 (0.06)	0.110 (0.096-0.126)	1 (0.07)	0.092 (0.076-0.111)	

Others and haemopoietic (190-208)	8 (0.25)	0.441 (0.391-0.497)	3 (0.20)	0.276 (0.227-0.335)	0.687 (0.270-1.746)
Haemopoietic (200-208)	2 (0.06)	0.110 (0.096-0.126)	1 (0.07)	0.092 (0.076-0.111)	
Brain (191)	1 (0.03)	0.055 (0.049-0.062)	0 (0.00)	-	
Thyroid and other endocrine (193-194)	4 (0.12)	0.220 (0.198-0.246)	0 (0.00)	-	

a. Incidence rate expressed per 1000 person-years.

b. Weighted by IPTW and adjusted for the usage of NSAID, aspirin, COX-2 inhibitor, ACEI/ARB, metformin, sulfonylurea, systemic steroid, and statin.

Table DS4 Baseline characteristics of study groups (this is a more detailed version of Table 1 in the main text)

	Anticonvulsant- only group (<i>n</i> =3250)	Lithium-only group (<i>n</i> =370)	Lithium- anticonvulsant group	<i>P</i>
Follow-up, years: median, IQR	5.2 (3.1–7.8)	7.1 (4.7–9.9)	7.5 (5.1–9.9)	<0.001
Cancer event, <i>n</i> (%)	86 (2.6)	6 (1.6)	23 (2.1)	0.324
Censored				
Death	163 (5.0)	14 (3.8)	56 (5.0)	
Disenrollment	87 (2.7)	11 (3.0)	13 (1.2)	
End of study period	2914 (89.7)	339 (91.6)	1017 (91.7)	
Male, <i>n</i> (%)	1327 (40.8)	159 (43.0)	480 (43.2)	0.328
Age, mean (s.d.)	45.9 (17.5)	38.5 (13.9)	37.1 (13.7)	<0.001
Median, IQR	44 (31–59)	37.5 (27–47)	35 (26–46)	<0.001
Charlson Comorbidity Index, <i>n</i> (%)				
0	2116 (65.1)	303 (81.9)	870 (78.4)	<0.001
1	638 (19.6)	46 (12.4)	161 (14.5)	
2	267 (8.2)	15 (4.1)	41 (3.7)	
≥3	229 (7.0)	6 (1.6)	37 (3.3)	
Mean (s.d.)	0.63 (1.11)	0.26 (0.66)	0.34 (0.80)	<0.001
Psychiatric comorbidity, <i>n</i> (%)				
Alcohol-use disorders	85 (2.6)	12 (3.2)	50 (4.5)	0.007
Substance use disorders	50 (1.5)	10 (2.7)	23 (2.1)	0.177
Depression	923 (28.4)	109 (29.5)	376 (33.9)	0.003
Anxiety	659 (20.3)	62 (16.8)	196 (17.7)	0.068
Schizophrenia	210 (6.5)	33 (8.9)	156 (14.1)	<0.001
Other psychosis	104 (3.2)	17 (4.6)	61 (5.5)	0.002
Physical comorbidity, <i>n</i> (%)				

Myocardial infarction	16 (0.5)	2 (0.5)	2 (0.2)	0.293
Congestive heart failure	57 (1.8)	1 (0.3)	1 (0.1)	<0.001
Hypertension	691 (21.3)	28 (7.6)	97 (8.7)	<0.001
Arrhythmias	107 (3.3)	5 (1.4)	27 (2.4)	0.058
Other acute ischemic heart disease	79 (2.4)	3 (0.8)	17 (1.5)	0.039
Other chronic ischemic heart disease	190 (5.9)	8 (2.2)	22 (2.0)	<0.001
Cerebrovascular disease	250 (7.7)	7 (1.9)	27 (2.4)	<0.001
Dementia	82 (2.5)	3 (0.8)	11 (1.0)	0.002
Chronic pulmonary disease	268 (8.3)	19 (5.1)	65 (5.9)	0.007
Connective tissue disease	47 (1.5)	4 (1.1)	7 (0.6)	0.100
Diabetes mellitus	352 (10.8)	20 (5.4)	61 (5.5)	<0.001
Moderate/severe renal disease	55 (1.7)	0 (0.0)	13 (1.2)	0.024
Moderate/severe liver disease	6 (0.2)	0 (0.0)	3 (0.3)	0.742
Dyslipidemia	268 (8.3)	9 (2.4)	55 (5.0)	<0.001
Obesity	9 (0.3)	0 (0.0)	5 (0.5)	0.441
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Comedication, n (%)				
Non-steroid anti-inflammatory drugs	2145 (66.0)	315 (85.1)	987 (89.0)	<0.001
cyclo-oxygenase-2 inhibitor	102 (3.1)	5 (1.4)	22 (2.0)	0.030
Aspirin	286 (8.8)	29 (7.8)	92 (8.3)	0.753
Angiotensin-converting enzyme/inhibitor/angiotensin receptor blocker	294 (9.1)	29 (7.8)	83 (7.5)	0.240
Statin	142 (4.4)	10 (2.7)	34 (3.1)	0.070
Metformin	271 (8.3)	13 (3.5)	44 (4.0)	<0.001
Sulfonylurea	297 (9.1)	16 (4.3)	47 (4.2)	<0.001
Systemic steroid	1044 (32.1)	144 (38.9)	492 (44.4)	<0.001
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Psychotropic agents				
First-generation antipsychotics	1453 (44.7)	150 (40.5)	614 (55.4)	<0.001
Second-generation antipsychotics	1224 (37.7)	144 (38.9)	575 (51.9)	<0.001

Tricyclic antidepressants	640 (19.7)	38 (10.3)	167 (15.1)	<0.001
Selective serotonin reuptake inhibitors	1217 (37.5)	156 (42.2)	478 (43.1)	0.002
Other antidepressants	1157 (35.6)	108 (29.2)	379 (34.2)	0.044
Anxiolytics/hypnotics	2878 (88.6)	299 (80.8)	952 (85.8)	<0.001
