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Supplementary Table 7. Results from E-value analysis

**Supplementary Table 1. Psychotropic medications included in the study**

|  |  |
| --- | --- |
| Category | Drug name |
| Lithium | Lithium carbonate |
| Lithium sulphate |
| Antipsychotics | Amisulpride |
| Aripiprazole |
| Asenapine |
| Chlorpromazine |
| Clopenthixol |
| Clozapine |
| Droperidol |
| Fluphenazine |
| Flupentixol |
| Haloperidol |
| Lurasidone |
| Molindone |
| Olanzapine |
| Paliperidone |
| Pericyazine |
| Perphenazine |
| Pimozide |
| Quetiapine |
| Risperidone |
| Sertindole |
| Sulpiride |
| Thioridazine |
| Trifluoperazine |
| Ziprasidone |
| Zuclopenthixol |
| Mood stabilizing antiepileptics | Carbamazepine |
| Lamotrigine |
| Valproate sodium |
| Antidepressants | Amineptine |
| Amitriptyline |
| Clomipramine |
| Dothiepin |
| Doxepin |
| Imipramine |
| Maprotiline |
| Mianserin |
| Motival |
| Nortriptyline |
| Protriptyline |
| Trazodone |
| Trimipramine |
| Moclobemide |
| Phenelzine |
| Citalopram |
| Escitalopram |
| Fluoxetine |
| Fluvoxamine |
| Paroxetine |
| Sertraline |
| Agomelatine |
| Bupropion |
| Desvenlafaxine |
| Milnacipran |
| Mirtazapine |
| Nefazodone |
| Oxitriptan |
| Venlafaxine |
| Vortioxetine |
| Duloxetine |
| Tianeptine |
| Benzodiazepine derivatives | Flunitrazepam |
| Flurazepam |
| Lormetazepam |
| Midazolam |
| Nitrazepam |
| Temazepam |
| Triazolam |
| Alprazolam |
| Bromazepam |
| Chlordiazepoxide |
| Diazepam |
| Lorazepam |
| Prazepam |
| Pinazepam |
| Clobazam |
| Clonazepam |
| Dipotassium clorazepate |
| Loprazolam |
| Estazolam |
| Quazepam |
| Oxazepam |

**Supplementary Table 2. Selection criteria of traumatic injuries cases at the emergency room setting in public hospitals in Hong Kong**

In Hong Kong, it is a compulsory standard procedure that the clinicians and trauma nurses at the emergency room settings in the public hospitals to identify the traumatic injuries cases based on the National Trauma Data Standard Patient Inclusion Criteria by the American College of Surgeons Committee on Trauma (American College of Surgeons Committee on Trauma, 2019).

|  |  |
| --- | --- |
| **Inclusion criteria 1: at least one of the following injury diagnostic codes** | |
| Description | ICD-10-CM codes |
| Types of injuries:   1. Open wound 2. Fracture 3. Dislocation and sprain of joints and ligaments 4. Injury of nerve 5. Injury to blood vessels 6. Injury to muscle, fascia and tendon, internal organs 7. Crushing injury 8. Avulsion and traumatic amputation 9. Other and unspecified injuries   Injuries to different body parts, including:   1. Head 2. Neck 3. Thorax 4. Abdomen, lower back, lumbar spine, pelvis and external genitals, 5. Shoulders and upper arm, 6. Elbow and forearm, 7. Wrist, hand and fingers 8. Hip and thigh 9. Knee and lower leg 10. Ankle and foot | S00-S99 with 7th character modifiers of A, B, or C only |
| Injuries involving multiple body regions | T07 |
| Injury of unspecified body region | T14 |
| Burns and corrosions of external body surface, eyes and internal organs, specified by site | T20-T28 with 7th character modifier of A only (burns by specific body parts – initial encounter) |
| Burns and corrosions of multiple and unspecified body regions | T30-T32 (burn by TBSA percentages) |
| Traumatic compartment syndrome of different body parts | T79.A1-T79.A9 with 7th character modifier of A only (Traumatic Compartment Syndrome –  initial encounter) |
| **Inclusion criteria 2: hospital admission or death** | |
| * Hospital admission diagnosis defined by trauma registry inclusion criteria; or * Patient transfer from one hospital to another hospital; or * Death resulting from the traumatic injury | -- |
| **Exclusion criteria 1: Superficial injuries** | |
| Superficial injuries of different body parts | S00, S10, S20, S30, S40, S50, S60, S70, S80, S90 |

**Reference**

American College of Surgeons Committee on Trauma. (2019). National Trauma Data Standard Data Dictionary 2019 Admissions. Retrieved from <https://www.facs.org/~/media/files/quality%20programs/trauma/ntdb/ntds/data%20dictionaries/ntdb_data_dictionary_2019_revision.ashx>

**Supplementary Table 3. Description of sensitivity analyses**

Several sensitivity analyses were planned to test the validity and robustness of the initial study results.

|  |  |  |
| --- | --- | --- |
| No. | Sensitivity analysis | Details |
| 1 | Redefining the start of the observation period to 1st January 2001, the 18th birthday of the individual, the date of the patient entering the database, or the first observed date of bipolar disorder diagnosis, whichever was later | Individuals might receive less medical attention before the diagnosis of bipolar disorder and the prescribing pattern might be different. |
| 2 | Removing patients who died during the observation period | Since traumatic injuries carry high risk of mortality, the observation period could be censored as a direct result of the traumatic injuries, causing bias to the results in both directions (under- or over-estimating the benefits of pharmacological treatment). A total of 702 patients with ER admissions due to traumatic injuries died during the observation period but there were no clustering of death shortly after the events. This will assess the effect of death on the results. |
| 3 | Removing patients with exposure to pharmacological treatment of bipolar disorder before the start of the observation period | As the self-controlled case series compared the incidence within an individual, included individuals were not necessary to be incident users of the treatment. This will assess this potential effect. |
| 4 | Removing patients with schizophrenia diagnosis (ICD-9-CM: 295) between the database inception and the end of observation period | Since there is some debate as to whether schizophrenia and bipolar disorder can be truly comorbid, removing patients who ever received schizophrenia diagnosis can ensure the patients who were truly diagnosed with bipolar disorder. |
| 5 | Redefining the study cohort by 1) including patients who had at least 2 hospitalization record with a diagnosis of bipolar disorder and 2) excluding those who had more than 1 schizophrenia related hospitalization record | A previous validation study, which validated the diagnosis of bipolar disorder in Swedish national registry, suggested the use of search algorithm based on at least 2 inpatient episodes of bipolar disorder and exclude patients with more than 1 inpatient episode of schizophrenia could improve sensitivity and specificity (Sellgren, Landén, Lichtenstein, Hultman, & Långström, 2011). To ensure patients included in our cohort were diagnosed with bipolar disorder, we applied the same criteria to define the study cohort. |
| 6 | Removing patients with event happening on the first day of treatment | As the exact time of the event is not available in the database, it is difficult to determine if the event occurred before or after the treatment initiation. |
| 7 | Adjusting for age, concurrent use of antidepressants, benzodiazepine derivatives. hypnotics and anxiolytics as time-varying confounders | As a previous study found an association between the risk of road accidents and use of anxiolytics (Ravera, van Rein, de Gier, & de Jong-van den Berg, 2011), it is possible that hypnotics and anxiolytics affect cognitive ability and hence causes traumatic injuries due to road accidents. |
| 8 | Adjusting for age, concurrent use of antidepressants and benzodiazepine derivatives, doses of treatment agents as time-varying confounders | Since varying dose of mood stabilizing treatment infers the changing severity of illness of bipolar disorder and changing dose of mood stabilizing treatment might also affect the prescribing of treatment regimen, doses of mood stabilizing agents can be a possible confounder.  To examine the effect of dose, we calculated the sum of total doses within the same exposure period using the ratio of prescribed daily dose to defined daily dose and the duration of exposure period. Then we further separated the exposure periods (for both acute and maintenance treatment) into low and high doses (above or below the median). |
| 9 | Different drug non-adherence scenarios | Each exposed period was further extended by adding 1 to 10 weeks after the end of an exposed period to assess this effect. |
| 10 | Computing E-value, which is defined as the minimum strength of association that an unmeasured confounder would need to have with both treatment and outcome to nullify the observed association. | Since there might be some time-varying unmeasured confounding factors which might potentially cause bias to the results, an E-value can quantify the minimum strength of association that an unmeasured confounder could have to affect the observed results. |

**References**

Ravera, S., van Rein, N., de Gier, J. J., & de Jong-van den Berg, L. T. (2011). Road traffic accidents and psychotropic medication use in The Netherlands: a case-control study. *British Journal of Clinical Pharmacology, 72*(3), 505-513. doi:10.1111/j.1365-2125.2011.03994.x

Sellgren, C., Landén, M., Lichtenstein, P., Hultman, C. M., & Långström, N. (2011). Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. *Acta Psychiatrica Scandinavica, 124*(6), 447-453. doi:10.1111/j.1600-0447.2011.01747.x

**Supplementary Table 4. Results of subgroup analysis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Risk periods** | **No. of events** | **Patient years** | **Crude incidence (per 100 patient-years)** | **Adjusted IRRa (95% CI)** | **P-value** |
| **Lithium** | | | | | |
| Baselineb | 4461 | 71455.31 | 6.24 | 1.00 | -- |
| Pre-exposure period | 31 | 127.24 | 24.36 | 1.27 (0.87-1.87) | 0.2166 |
| Acute treatment | 41 | 633.68 | 6.47 | 0.67 (0.48-0.94) | 0.0208 |
| Maintenance treatment | 480 | 9734.97 | 4.93 | 0.81 (0.70-0.94) | 0.0046 |
| Post-exposure period | 27 | 303.39 | 8.90 | 1.20 (0.80-1.78) | 0.3811 |
| **Antipsychotics** | | | | | |
| Baselineb | 2929 | 45466.13 | 6.37 | 1.00 | -- |
| Pre-exposure period | 130 | 354.54 | 36.67 | 3.74 (3.04-4.58) | <.0001 |
| Acute treatment | 213 | 2264.49 | 9.41 | 1.43 (1.20-1.70) | <.0001 |
| Maintenance treatment | 1683 | 33006.27 | 5.10 | 1.00 (0.90-1.10) | 0.9631 |
| Post-exposure period | 85 | 1163.15 | 7.31 | 1.16 (0.91-1.47) | 0.2359 |
| **Mood stabilizing antiepileptics (i.e. valproate, carbamazepine and lamotrigine)** | | | | | |
| Baselineb | 3610 | 55258.02 | 6.53 | 1.00 | -- |
| Pre-exposure period | 71 | 286.95 | 24.74 | 1.90 (1.46-2.47) | <.0001 |
| Acute treatment | 140 | 1674.49 | 8.36 | 1.17 (0.95-1.43) | 0.1343 |
| Maintenance treatment | 1173 | 24269.04 | 4.83 | 0.99 (0.90-1.10) | 0.9218 |
| Post-exposure period | 46 | 766.08 | 6.00 | 1.00 (0.73-1.38) | 0.9835 |
| Other medications adjusted (as time-varying factor) | | | | | |
| Antidepressants during treatment | 934 | 16187.31 | 5.77 | 1.08 (0.98-1.20) | 0.1288 |
| No antidepressants | 4106 | 66067.27 | 6.21 | 1.00 | -- |
| Benzodiazepine derivatives during treatment | 878 | 14845.54 | 5.91 | 1.27 (1.15-1.41) | <.0001 |
| No benzodiazepine derivatives | 4162 | 67409.04 | 6.17 | 1.00 | -- |

aAll estimates are adjusted for age in one-year age band and concurrent use of antidepressants, benzodiazepine derivatives, and/or different classes of treatment agents (i.e. lithium, antipsychotics, mood stabilizing antiepileptics).

bWhen stratifying by drug classes, baseline period refers to unexposed period to study drug class.

Abbreviations: CI=confidence interval; IRR=incidence rate ratio

**Supplementary Table 5. Results of sex stratified analysis**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No. of events** | **Adjusted IRRa (95% CI)** | **P-value** |
| Males (n=1919) | | | |
| Baseline | 963 | 1.00 | -- |
| Pre-exposure period | 66 | 5.49 (4.24-7.11) | <0.0001 |
| Acute treatment | 96 | 1.56 (1.23-1.97) | <0.0001 |
| Maintenance treatment | 764 | 0.95 (0.81-1.11) | 0.52 |
| Post-exposure period | 30 | 1.12 (0.77-1.64) | 0.54 |
| Females (n=3121) |  |  |  |
| Baseline | 1480 | 1.00 | -- |
| Pre-exposure period | 67 | 3.72 (2.90-4.78) | 0.001 |
| Acute treatment | 142 | 1.38 (1.14-1.67) | 0.001 |
| Maintenance treatment | 1365 | 0.98 (0.87-1.11) | 0.79 |
| Post-exposure period | 67 | 1.48 (1.15-1.91) | 0.002 |

aAll estimates are adjusted for age in one-year age band and concurrent use of antidepressants and/or benzodiazepine derivatives.

Abbreviations: CI=confidence interval; ER=emergency room; IRR=incidence rate ratio

**Supplementary Figure 1. Distribution of patients who died within 30 days after the first emergency room admissions due to traumatic injuries**

**Supplementary Table 6. Results from sensitivity analyses**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No. of events** | **Adjusted IRRa (95% CI)** | **P-value** |
| Sensitivity analysis 1: Study started on 1st January 2001, the 18th birthday of the individual, the date of the patient entering the database, or the first observed date of bipolar disorder diagnosis, whichever was later. (n=2634) | | | |
| Baseline | 537 | 1.00 | -- |
| Pre-exposure period | 28 | 4.57 (3.08-6.77) | <0.0001 |
| Acute treatment | 182 | 1.56 (1.28-1.91) | <0.0001 |
| Maintenance treatment | 1817 | 1.07 (0.92-1.25) | 0.37 |
| Post-exposure period | 70 | 1.51 (1.16-1.96) | 0.002 |
|  |  |  |  |
| Sensitivity analysis 2: Removing patients who died during the observation period (n=4338) | | | |
| Baseline | 2215 | 1.00 | -- |
| Pre-exposure period | 111 | 4.39 (3.61-5.34) | <0.0001 |
| Acute treatment | 198 | 1.35 (1.14-1.58) | <0.0001 |
| Maintenance treatment | 1737 | 0.88 (0.80-0.98) | 0.02 |
| Post-exposure period | 77 | 1.22 (0.96-1.54) | 0.10 |
|  |  |  |  |
| Sensitivity analysis 3: Restricting the cohort to incident users of treatment of mood stabilizers and/or antipsychotics (n=4843) | | | |
| Baseline | 2420 | 1.00 | -- |
| Pre-exposure period | 130 | 4.47 (3.73-5.36) | <0.0001 |
| Acute treatment | 233 | 1.48 (1.28 -1.72) | <0.0001 |
| Maintenance treatment | 1966 | 0.96 (0.87-1.05) | 0.36 |
| Post-exposure period | 94 | 1.37 (1.10-1.69) | 0.004 |
|  |  |  |  |
| Sensitivity analysis 4: Removing patients with schizophrenia between the database inception and the end of observation period (n=4365) | | | |
| Baseline | 2248 | 1.00 | -- |
| Pre-exposure period | 120 | 4.65 (3.85-5.62) | <0.0001 |
| Acute treatment | 208 | 1.55 (1.32-1.82) | <0.0001 |
| Maintenance treatment | 1705 | 0.97 (0.87-1.07) | 0.53 |
| Post-exposure period | 84 | 1.42 (1.14-1.78) | 0.002 |
|  |  |  |  |
| Sensitivity analysis 5: Redefining the study cohort by 1) including patients who had at least 2 hospitalization record with a diagnosis of bipolar disorder and 2) excluding those who had more than 1 schizophrenia related hospitalization record (n=2384) | | | |
| Baseline | 891 | 1.00 | -- |
| Pre-exposure period | 64 | 4.35 (3.35-5.65) | <0.0001 |
| Acute treatment | 129 | 1.35 (1.10-1.66) | 0.0045 |
| Maintenance treatment | 1246 | 0.96 (0.84-1.10) | 0.5687 |
| Post-exposure period | 54 | 1.39 (1.04-1.85) | 0.0247 |
|  |  |  |  |
| Sensitivity analysis 6: Removing patients in which the event happened on the first day of treatment (n=5017) | | | |
| Baseline | 2443 | 1.00 | -- |
| Pre-exposure period | 133 | 4.42 (3.69-5.28) | <0.0001 |
| Acute treatment | 215 | 1.29 (1.32-1.82) | 0.0001 |
| Maintenance treatment | 2129 | 0.96 (0.87-1.05) | 0.37 |
| Post-exposure period | 97 | 1.33 (1.08-1.64) | 0.007 |
|  |  |  |  |
| Sensitivity analysis 7: Adjusted for age, concurrent use of antidepressants, benzodiazepine derivatives. hypnotics and anxiolytics as time-varying confounders (n=5040) | | | |
| Baseline | 2443 | 1.00 | -- |
| Pre-exposure period | 133 | 4.41 (3.69-5.28) | <0.0001 |
| Acute treatment | 238 | 1.41 (1.21-1.63) | <0.0001 |
| Maintenance treatment | 2129 | 0.95 (0.86-1.05) | 0.2904 |
| Post-exposure period | 97 | 1.34 (1.09-1.66) | 0.0061 |
|  |  |  |  |
| Sensitivity analysis 8: Adjusted for age, concurrent use of antidepressants and benzodiazepine derivatives, doses of treatment agents as time-varying confounders (n=5040) | | | |
| Baseline | 2443 | 1.00 | -- |
| Pre-exposure period | 133 | 4.43 (3.70-5.30) | <0.0001 |
| Acute treatment: low dose | 167 | 1.41 (1.19-1.67) | <0.0001 |
| Acute treatment: high dose | 71 | 1.51 (1.18-1.95) | 0.0012 |
| Maintenance treatment: low dose | 254 | 1.11 (0.96-1.30) | 0.1618 |
| Maintenance treatment: high dose | 1875 | 0.94 (0.85-1.04) | 0.2288 |
| Post-exposure period | 97 | 1.34 (1.09-1.66) | 0.00061 |
|  |  |  |  |

aAll estimates are adjusted for age in one-year age band and concurrent use of antidepressants and/or benzodiazepine derivatives.

Abbreviations: CI=confidence interval; ER=emergency room; IRR=incidence rate ratio

**Supplementary Figure 2. Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio of emergency room admissions due to traumatic injuries in the pre-exposure period**

**Supplementary Figure 3. Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio of emergency room admissions due to traumatic injuries in the acute treatment**

**Supplementary Figure 4. Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio of emergency room admissions due to traumatic injuries in the maintenance treatment**

**Supplementary Figure 5. Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio of emergency room admissions due to traumatic injuries in the post-exposure period**

**Supplementary Table 7. Results from E-value analysis**

|  |  |  |
| --- | --- | --- |
| **Risk windows** | **Adjusted IRR (95% CI)** | **E-value (lower CI)** |
| Acute treatment | 1.44 (1.24-1.67) | 2.24 (1.79) |
| Maintenance treatment | 0.97 (0.88-1.06) | -- |
| Direct comparison of maintenance treatment with pre-exposure period | 0.22 (0.18-0.26) | 8.56 (7.15) |
| Direct comparison of maintenance treatment with acute treatment | 0.67 (0.59-0.77) | 2.35 (1.92) |
| Direct comparison of maintenance treatment with post-exposure period | 0.72 (0.58-0.89) | 2.12 (1.5) |

In our main analysis, the IRR (95% CI) for ER admissions due to traumatic injuries with the acute treatment was 1.44 (1.24-1.67). The E-value for the result point estimate was 2.24 with the lower confidence interval was 1.79 in an IRR scale. This result indicated that our observed increase in the risk of ER admissions due to traumatic injuries during the acute treatment could be explained away by an unmeasured time-varying confounder that was associated with both the treatment and the outcome by a risk ratio of 2.24 each; the confidence interval could be moved to include 1.00 (i.e. no association) by an unmeasured time-varying confounder that was associated with both the treatment and the outcome by a risk ratio of 1.79-fold each, with the existing confounders that were already accounted for, but weaker confounding could not do so.

During maintenance treatment, the IRR for ER admissions due to traumatic injuries did not reach statistical significance so the E-value was not calculated.

The E-value for the result point estimates of the direct comparison of different risk windows with the maintenance treatment for the ER admissions due to traumatic injuries were calculated. Similar to the main analysis, the calculated E-value (from 2.12 to 8.56) and lower confidence interval (from 1.5 to 7.15) explained the minimum strength of an unmeasured time-varying confounder that would nullify the observed decreased risk of ER admissions due to traumatic injuries with the use of pharmacological treatment of BPD.

Therefore, it is unlikely that an unmeasured time-varying confounder with this large magnitude of an association with both receiving pharmacological treatment of BPD and risk of ER admissions due to traumatic injuries exists, as such magnitude is much larger than those risk factors for ER admissions due to traumatic injuries, in particular age, concurrent use of psychotropic medications, for which we have already controlled for in the analyses. Therefore, our result is unlikely to have been due to an unmeasured time-varying confounder and this further supports the validity of our result.