Title: Association between the pharmacological treatment of bipolar disorder and risk of traumatic injuries: A self-controlled case series study

Running title: Treatment of bipolar disorder and traumatic injuries

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Abstract (250/250)

Background: Patients with bipolar disorder (BPD) are prone to engage in risk-taking behaviours and self-harm, contributing to higher risk of traumatic injuries requiring medical attention at the emergency room (ER).We hypothesize that pharmacological treatment of BPD could reduce the risk of traumatic injuries by alleviating symptoms but evidence remains unclear. This study aimed to examine the association between pharmacological treatment and the risk of ER admissions due to traumatic injuries.

Methods: Individuals with BPD who received mood stabilizers and/or antipsychotics were identified using a population-based electronic healthcare records database in Hong Kong (2001-2019)**.** A self-controlled case series design was applied to control for time-invariant confounders.

Results: A total of 5040 out of 14021 adults with BPD who received pharmacological treatment and had incident ER admissions due to traumatic injuries from 2001-2019 were included. An increased risk of traumatic injuries was found 30 days before treatment (Incidence rate ratio (IRR) 4.44 (3.71-5.31), p<0.0001). After treatment initiation, the risk remained increased with a smaller magnitude, before returning to baseline (IRR 0.97 (0.88-1.06), p=0.50) during maintenance treatment. The direct comparison of the risk during treatment to that before and after treaetment showed a significant decrease. After treatment cessation, the risk was increased (IRR 1.34 (1.09-1.66), p=0.006).

Conclusions: This study supports the hypothesis that pharmacological treatment of BPD was associated with a lower risk of ER admissions due to traumatic injuries but an increased risk after treatment cessation. Close monitoring of symptoms relapse is recommended to clinicians and patients if treatment cessation is warranted.

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INTRODUCTION

Bipolar disorder (BPD) is a severe mental illness, which is associated with high rates of morbidities and mortality (Crump, Sundquist, Winkleby, & Sundquist, 2013). It is characterized by recurrent mood fluctuations, agitation, impulsiveness, poor concentration, and inattention. BPD can pose a significant impact on physical health, cognitive and psychomotor functions, as well as relationships with their families and friends. Patients with BPD often repeatedly visit the emergency room (ER) due to various reasons, in which traumatic injuries are one of the most alarming causes for admissions (Slankamenac, Heidelberger, & Keller, 2020).

It has been well recognized that patients with BPD are prone to perform risk-taking behaviors, such as aggressive behaviors to self or others, violence, suicidal attempts, and dangerous driving, under the influence of impulsivity (Látalová, 2009; Najt et al., 2007). Impulsive aggression usually arises during the manic or hypomanic phase while the risk of self-harm and/or suicidal attempts is higher during depressive episodes (Látalová, 2009; Valtonen et al., 2008). Impaired concentration and attention also adversely affect patients' abilities to perform daily tasks and put them at risk of accidents. All these symptoms ultimately increase the tendency of physical injuries or traumatic injuries that result in ER admissions. Prior studies also showed that patients with BPD have elevated risks of medically attended injuries, motor vehicle accidents, self-harm, and suicidal attempts than those without BPD (Chen et al., 2018; McGinty, Baker, Steinwachs, & Daumit, 2013; Singhal, Ross, Seminog, Hawton, & Goldacre, 2014). All of these traumatic injuries could potentially contribute to the heightened risk of premature death among patients with BPD, where the unnatural death (including accidents, suicide completion, intentional and unintentional injuries) is reported to be 7 times more common in patients with BPD relative to the general population, as well as substantial physical disabilities and financial burdens in both individual and population levels (Dean, Gerner, & Gerner, 2004; Hayes, Miles, Walters, King, & Osborn, 2015). Therefore, effective strategies are necessary to reduce the occurrence of traumatic injuries.

Numerous studies including randomized clinical trials and observational studies of mood stabilizers (e.g. lithium, valproate, lamotrigine, and carbamazepine) and antipsychotics have demonstrated beneficial effects on relapse prevention, hospitalizations, and mood stabilization compared to placebo or active comparators (Kishi et al., 2021; Lähteenvuo et al., 2018; Miura et al., 2014; Weisler, Kalali, & Ketter, 2004). Thus, we hypothesize that the pharmacological approaches could lower the risks of traumatic injuries by alleviating symptoms and stabilizing mood. Despite the limited studies conducted on the outcome of traumatic injuries, most published studies have primarily focused on evaluating the effect of drug treatment of BPD on different causes of injuries, such as traffic accidents, violent behaviour, self-harm, and suicidal attempts, which provided no concise conclusion (Chen et al., 2018; Fazel, Zetterqvist, Larsson, Långström, & Lichtenstein, 2014; Hayes et al., 2016). However, the effects of the pharmacological treatment of BPD on the overall risk of ER admissions due to traumatic injuries have been under-examined in this regard. In this study, we aimed to assess the association between the pharmacological treatment of BPD and risks of ER admissions due to traumatic injuries, to test our hypothesis that the drug treatment of BPD has a protective effect on traumatic injuries.

METHODS

Data Source

Clinical Data Analysis Reporting System (CDARS) is a population-based electronic health record database developed by the Hong Kong Hospital Authority (HA), which is the sole acute public healthcare services provider including mental health. HA services are available to all Hong Kong residents (>7.4 million) (Hospital Authority, 2021). Clinical data in CDARS has been continuously updated for each individual who assessed public services and includes medical diagnosis, prescriptions and dispensing records, accidents and emergency attendances, hospital admissions and discharges medical records, psychiatric outpatient and inpatients medical records, as well as all other specialist outpatients and general outpatients medical records. CDARS does not capture clinical data from the private healthcare sectors but a local study reported that approximately 88.5% of psychiatric patients utilised public mental health services under HA (Tang, 1997). Therefore, the CDARS is

likely to cover the majority of the Hong Kong population. Since all medical information is directly recorded from health records to CDARS, the accuracy of data has been guaranteed and therefore successfully used in several pharmaco-epidemiological studies in psychotropic medications (K. K. Man et al., 2015; K. K. C. Man et al., 2017; Wang et al., 2021; Wong et al., 2016). This retrospective study used CDARS as a longitudinal electronic healthcare record database. Therefore, follow-up assessment were based on the records of the medical care provided by the HA. The clinical information in the baseline, as well as the follow-up, was extracted from CDARS. The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW19-409).

Study Design

A self-controlled case series (SCCS) design was applied to investigate the association between the pharmacological treatment of BPD and ER admissions due to traumatic injuries, by making within-individual comparisons in individuals who have experienced both exposures and outcomes of interests over the observation period. Each individual serves as their own control by comparing exposed and unexposed periods, rather than exposed and unexposed patients (Gao et al., 2021; K. K. C. Man et al., 2020). In contrast to between-individual comparison study designs such as cohort and case-control studies, SCCS can eliminate the potential effects of recorded and unmeasured time-invariant confounding factors, such as genetic factors, childhood experience, family history and underlying disease severity (Petersen, Douglas, & Whitaker, 2016).

Case Identification

Individuals diagnosed with BPD from database inception to 31st December 2019 were identified in CDARS. The diagnosis of BPD was identified through the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes (296.0, 296.1, and 296.4-296.8). Patients with the diagnosis of schizophrenia or schizoaffective disorder (ICD-9-CM: 295) after the diagnosis of BPD were excluded. CDARS contains hospital inpatient and outpatient specialist clinical services and mental disorders diagnoses are normally made by psychiatrists. Among all patients with

BPD, those aged 18 or above who received at least one prescription of any of the BPD pharmacological treatment agents (lithium, valproate, carbamazepine, lamotrigine, and/or antipsychotics) and had at least one ER admission due to traumatic injuries during the study period (from 1st January 2001 to 31st December 2019) were included in the analyses.

As BPD is rarely diagnosed in children and adolescents (NICE, 2014), patients were included if they were aged 18 years or above. Therefore, the individual observation period started on 1st January 2001, the 18th birthday of the patient, or the date of the patient entering the database (whichever was later) and ended on 31st December 2019 or the date of registered death (whichever was earlier). To fulfill the assumptions of SCCS, patients who had experienced the outcome of interest before the observation started were excluded. In SCCS, there was no censoring by the outcome of interest as this would violate the model assumptions and introduce bias to the results (K. K. C. Man et al., 2017; Petersen et al., 2016).

Exposures and Outcomes

The exposure of interest was the pharmacological treatment of BPD including mood stabilizers and/or antipsychotics. Mood stabilizers are defined as lithium, sodium valproate, carbamazepine, and lamotrigine only. These drugs were chosen because they are recommended by the international clinical guidelines and are commonly used as the treatment of BPD in Hong Kong (Malhi et al., 2021; Ng et al., 2021; NICE, 2014; Yatham et al., 2018). Details of the study medications were summarized in Supplementary Table 1. Exposure periods were defined as the time receiving the study medications estimated by prescription start and end dates recorded in CDARS for each prescription. More than 99% of the prescriptions have the intended prescription start and end dates available. The dispensing dates were automatically recorded when patients have their prescriptions dispensed at the pharmacies at the public hospitals. The duration of treatment was calculated using daily dosages and quantity prescribed if prescription end dates were not available. The median duration of different drug classes was then imputed for those prescriptions with insufficient drug details. We divided the observation period into five different risk windows: 1) absence of all study medications (baseline period), 2) 30 days before the first study medication exposure (pre-exposure period), 3) first 30 days

of study medications exposure (acute treatment), 4) day 31 till the end of study medications exposure (maintenance treatment), and 5) 30 days after the end of exposure of study medications (post-exposure period). A pictorial representation of the study design timeline of a single hypothetical participant is illustrated in Figure 1a. The pre-exposure period was defined as the time before the first prescription of study medications (lithium, valpraote, carbamazepine, lamotrigine, or antipsychotics) so there were no pre-exposure periods before each of the maintenance treatment periods. The reason for adding a 30-day pre-exposure period was to address any effects of recent ER admissions which might alter the likelihood of prescribing treatment of BPD and potentially introduce bias to the risk estimates during the treatment.

The outcome of interest was incident ER admission due to traumatic injuries. In Hong Kong, clinicians define ER admissions due to traumatic injuries according to National Trauma Data Standard Patient Inclusion Criteria and coded as "Traumatic case=Yes" in CDARS as a compulsory procedure upon admission and are validated by the ER clinicians and nurses (Supplementary Table 2) (American College of Surgeons Committee on Trauma, 2019). The corresponding date of the ER admission was identified as an event date.

Statistical Analysis

Incidence rate ratios (IRRs) with 95% confidence intervals (CI) were estimated by comparing the incidence rates of outcomes during different periods with the rate during the baseline period using conditional Poisson regression. A significance level <.05 was used in all statistical analyses. We adjusted for age in one-year age bands and concurrent use of antidepressants and/or benzodiazepines derivatives as time-varying confounding factors. The analysis was further stratified by sex.

A subgroup analysis was conducted by stratifying by different drug classes (i.e. lithium, antipsychotics, mood stabilizing antiepileptics), we considered different pharmacological agents (other than the study drug class) as time varying exposures (Figure 1b). Patients who had ER admissions due to traumatic injuries without exposure to the study drug class during the observation period were included to contribute information on the impact of time-varying confounders on the risk

of ER admissions due to traumatic injuries (Whitaker, Hocine, & Farrington, 2009). All unexposed person-time to the respective study drug class was included in the baseline period . The inclusion of unexposed cases is recommended when the exposure periods are long or indefinite (Whitaker et al., 2009).

To test the robustness and validity of the study results, several sensitivity analyses were conducted with different definitions of study cohort, criteria of defining observation period, and lengths of exposure periods including 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 BPD diagnosis, whichever was later; 2) removing individuals who died during the observation period; 3) restricting the study cohort to incident users of mood stabilizers and/or antipsychotics; 4) restricting to individuals without a diagnosis of schizophrenia from database inception till the end of observation period; 5) redefining the study cohort by only including patients with at least 2 inpatient diagnosis of BPD and excluding those with more than 1 inpatient diagnosis of schizophrenia from database inception till the end of observation period; 6) removing individuals with ER admission due to traumatic injuries happening on the first day of prescription of any study medications; and 7) different drug non-adherence scenarios. To account for any potential residual confounding, an E-value estimates the required strength of an unmeasured confounding variable that would nullify the observed associations between our exposure and outcomes, while accounting for all measured covariates (VanderWeele & Ding, 2017). We also further adjusted for some potential confounders, such as concurrent use of hypnotics and anxiolytics and doses of treatment agents in two separate sensitivity analyses. The purpose and details of each sensitivity analysis were reported in Supplementary Table 3. All analyses were performed by two investigators (VN and LG) for quality assurance using SAS (version 9.4) and R (version 3.5.3; R Core Team) respectively.

RESULTS

Among 14021 patients with BPD who received at least one prescription of mood stabilizers and/or antipsychotics between the observation period, 5040 of them were identified with incident ER admissions due to traumatic injuries and included in the analysis (Figure 2). The overall incidence rate

of ER admissions due to traumatic injuries among patients who received mood stabilizing treatment during the observation period was 4.79 per 100 patient-years. The mean age at the start of the observation period is 38.1 years old and the mean duration of follow-up is 16.3 years (Table 1).

Compared to the baseline period, the risk of ER admissions due to traumatic injuries was approximately 4.4-fold higher during the pre-exposure period (IRR=4.44, 95% CI 3.71-5.31, p<0.0001) and then was lowered to IRR of 1.44 (95% CI 1.24-1.67, p<0.0001) immediately after the treatment was initiated (Table 2). The risk became similar to the baseline level during maintenance treatment (IRR=0.97, 95% CI 0.88-1.06, p=0.50) but increased after the treatment was ceased (IRR=1.34, 95% CI 1.09-1.66, p=0.006). However, when we directly compared the maintenance treatment to other risk periods (pre-exposure, acute treatment and post-exposure periods respectively), we also observed a reduction in the risk of ER admissions due to traumatic injuries during the maintenance treatment (pre-exposure: IRR=0.22, 95% CI 0.18-0.26, p<0.0001; acute treatment: IRR=0.67, 95% CI 0.59-0.77, p<0.0001; post-exposure: IRR=0.72, 95% CI 0.58-0.89, p=0.002).

When stratifying by different drug classes, an increased risk was only observed in pre-exposure periods to antipsychotics and mood stabilizing antiepileptics (antipsychotics: IRR=3.74, 95% CI 3.04-4.58, p<0.0001; mood stabilizing antiepileptics: IRR=1.90, 95% CI 1.46-2.47, p<0.0001) (Supplementary Table 4). Compared to their own baseline periods, lithium use was associated with a lower risk during both acute (IRR=0.67; 95% CI 0.48-0.94, p=0.0208) and maintenance treatment (IRR=0.81, 95% CI 0.70-0.94, p=0.0046) while an increased risk with decreasing magnitude was detected with the use of antipsychotics during acute treatment (IRR=1.43, 95% CI 1.20-1.70, p<0.0001). No significant changes in the risk was found with the use of mood stabilizing antiepileptics (acute treatment: IRR=1.17, 95% CI 0.95-1.43, p=0.1343; maintenance treatment: IRR=0.99, 95% CI 0.90-1.10, p=0.9218).

Further analysis using non-parametric spline-based SCCS showed that the risk of ER admissions due to traumatic injuries increased significantly before the treatment initiation and then started to drop to the baseline level within 30 days after the treatment was started (Figure 3). The sex-stratified analysis showed similar results to the overall analysis (Supplementary Table 5). A total of 44 patients (0.87%)

died within 30 days after the incident ER admissions due to traumatic injuries and the distribution of the proportion of patients who censored the observation period within 30 days after the first ER admissions due to traumatic injuries were shown in Supplementary Figure 1. We removed these patients who died during the observation period in sensitivity analysis and the results remained robust. The remaining sensitivity analyses did not change the overall findings (Supplementary Table 6-7, Supplementary Figures 2-5).

DISCUSSION

From the main analysis, the incidence of ER admissions due to traumatic injuries demonstrated a 4.4-fold and 1.4-fold elevation 30 days before and after the initiation of the pharmacological treatment of BPD, respectively. During the prolonged treatment (greater than one month), the risk returned to the baseline. Considering the analysis of the direct comparison of the incidence rate during the treatment periods to the pre-exposure periods, our study results do not suggest an increased risk of ER admissions due to traumatic injuries associated with the use of BPD pharmacological treatment. When stratifying by different drug classes, lithium was associated with a lower risk while an increased risk with decreasing magnitude was observed during acute treatment of antipsychotics. No significant changes were detected with the use of mood stabilizing antiepiletpics.

Indeed, the 30-day pre-exposure period showed a high incidence of ER admissions due to traumatic injuries. This suggests that the observed increased risk of traumatic injuries before initiation was due to the worsening symptoms, recurrent mood episodes or agitation that lead to medical attention and hence clinicians decide to start the treatment. However, our non-parametric plot (Figure 3) showed a sudden drop of IRR around 20 days before treatment initiation. One possible reason to explain is that patients with worsening symptoms or fluctuated mood episodes could potentially receive more care and support from family and peers or psychotherapy from healthcare professionals before being medicated, leading to a temporary decrease in IRR. Prolonged exposure to BPD treatments (greater than one month) was associated with a significantly lower risk of ER admission due to traumatic injuries relative to the pre-exposure period. Although the incidence for ER admissions due to traumatic injuries rose shortly after treatment cessation, the magnitude of the increased risk was lower

than that during the pre-exposure period. Our overall findings support the hypothesis that BPD treatment together with other medical care could lower the risk of traumatic injuries in patients with BPD.

Discontinuation of long-term psychotropic medications regimen has been a common clinical occurrence among patients with BPD and is usually followed by a range of withdrawal reactions that could arise within hours or days (Cosci & Chouinard, 2020; Kishi et al., 2020). The earlier relapse of symptoms and reoccurrences of mood episodes have important clinical implications. A previously published systematic review and meta-analysis showed that the risks of any recurrent mood episodes (mania or depressive episodes) increased after discontinuation of mood stabilizing therapy, particularly the risk of the recurrent manic, hypomanic and/or mixed episodes increased immediately after treatment cessation while the recurrence of depressive episodes was delayed (Kishi et al., 2020). The cognitive and functional abilities might be more likely adversely affected under the influence of impulsivity during manic episodes and hence increasing the likelihood of risk-taking behaviour and accidents, thus the risk of traumatic injuries would possibly rebound as observed in our study. Although no significant changes were observed during the post-exposure periods of individual drug classes due to small sample, close monitoring of patients' symptoms is still highly recommended if treatment is discontinued by clinicians or patients themselves.

To our knowledge, no study has reported a direct association between the risk of traumatic injuries and use of pharmacological treatment of BPD. Limited studies have been conducted to examine the association of drug treatment of BPD and different causes of injuries, except for suicidal attempts. Similar to our findings, a previous study using primary care healthcare database from the United Kingdom reported that patients with BPD taking lithium had reduced rate of self-harm and unintentional injuries, implicating that lithium can reduce the impulsive aggression in addition to mood stabilization (Hayes et al., 2016). Most of the existing studies largely focussed on either the causes or types of traumatic injuries. Several studies demonstrated lithium had a decreasing tendency of road injuries, fractures and traumatic brain injuries but the results were not statistically significant, possibly due to small sample size (Chen et al., 2018; Liao et al., 2021; Su et al., 2017). Although our

study also revealed that lithium use was associated with a decreased risk of traumatic injuries, the aforementioned evidence could not be directly comparable to our findings. Further studies with a larger sample size are warranted to investigate the effect of individual psychiatric medication on ER admissions due to traumatic injuries to provide more evidence on the use of polypharmacy in the management of BPD.

Our study has notable strengths. SCCS study design relies on the within-individual comparison to control both measured and unmeasured time-invariant confounding factors. This could prevent the selection bias related to the control group in a cohort or case-control studies due to the nature of the between-individual comparison. Apart from the study design, the clinical records of ER attendances are not commonly available in electronic healthcare databases. Data used in our study directly comes from ER admission records and the date of event was automatically recorded into the system upon admission. Similarly, the medication data in CDARS are dispensing records, which the dispensing dates are automatically recorded. The majority of the dispensing records had the intended prescription start and end dates recorded. Therefore, the precise prescription periods and event dates, which are crucial to SCCS, could help maintain the accuracy of the results. Furthermore, the HA is the sole public healthcare service provider which manages the majority of patients who need specialist care in Hong Kong (Leung, Tin, & O'Donnell, 2009). Patients with BPD in our study were managed by the specialists at the hospitals and their diagnosis of BPD were confirmed for further clinical management so it is unlikely that there is a significant misdiagnosis compared to primary care electronic healthcare records and claims data, in which these databases frequently utilized external data, such as specialist letters and hospital discharge summary, for validation (Herrett, Thomas, Schoonen, Smeeth, & Hall, 2010).

There are some limitations to consider in our study. Firstly, the actual reasons or diagnoses for ER admissions are not well-recorded as ICD-9-CM code. Due to the data protection regulation, we are unable to access the free text to acertain the causes of ER admissions. Consequently, we are not able to identify the causes of patients admitted to ER and hence the nature of traumatic injuries. However, the aim of our study was to investigate the association between the treatment and ER admissions due

to traumatic injuries so the reasons for traumatic injuries are only of secondary interest. Secondly, like other observational studies using electronic databases, CDARS only provides medication prescribing and dispensing records but adherence to medications is not recorded. This might lead to misclassification of the exposure periods which would usually bias the estimates towards null and hence potentially masking the effect of the medications but one of our sensitivity analyses mimicked the scenarios of non-adherence by extending the exposure periods from 1-10 weeks and our results remained robust as the primary analysis. Furthermore, CDARS captures clinical data only from the public healthcare system in Hong Kong, so data from the private practice is not available and the exposure periods might be underestimated. Patients with higher socio-economic status might seek consultation and treatment from the physicians at private sector but patients with BPD usually require lifelong treatment and would often prefer public services due to subsidised medical costs (Leung et al., 2009). Therefore, our study likely covered most of the BPD patients in Hong Kong. Thirdly, the utilization of non-pharmacological treatment is not well-recorded in CDARS, therefore we would not be able to identify patients who received non-pharmacological treatment in our study cohort and hence they are not accounted for in our analysis. Such missing information might potentially bias the result estimates. However, non-pharmacological treatment is labour intensive. Subject to inadequacy of resources and manpower at the HA (Food and Health Bureau, 2017; Legislative Council Secretariat, 2020), it is uncommon for patients with BPD to be referred for non-pharmacological treatment. Furthermore, pharmacological treatment is considered as the mainstay approach for management of BPD according to international treatment guidelines, which most clinicians comply with. It is common that clinicians prescribe pharmacological treatment to patients when their presentations indicate mood disturbance or relapse due to crsis or negative experience for symptoms control then initiate non-pharmacological treatment only if the symptoms are not controlled and time permitted for counselling the patients. Therefore, it is unlikely that the effect of non-pharmacological treatment could affect the overall conclusion.

CONCLUSION

The risk of ER admissions due to traumatic injuries was higher before the start of treatment of BPD and decreased following treatment initiation, hence our study supports the hypothesis that the pharmacological treatment of BPD with appropriate medical care is associated with reduced risk of traumatic injuries, especially for lithium. This finding has important implications for clinical practice. Clinicians should be mindful of the timely prescribing of appropriate pharmacological regimens to patients based on their symptoms and severity; monitor for relapse of symptoms if the cessation of treatment is warranted.

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Ho Ming Edwin Lee, Joseph F Hayes, David P.J. Osborn and Timothy H. Rainer declare no conflict of interest.

Ethics standard

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW19-409).

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References

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

Chen, V. C., Yang, Y. H., Lee, C. P., Wong, J., Ponton, L., Lee, Y., . . . Wu, S. I. (2018). Risks of road injuries in patients with bipolar disorder and associations with drug treatments: A population-based matched cohort study. *Journal of Affective Disorders, 226*, 124-131. doi:10.1016/j.jad.2017.09.029

Cosci, F., & Chouinard, G. (2020). Acute and Persistent Withdrawal Syndromes Following Discontinuation of Psychotropic Medications. *Psychotherapy and Psychosomatics, 89*(5), 283-306. doi:10.1159/000506868

Crump, C., Sundquist, K., Winkleby, M. A., & Sundquist, J. (2013). Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. *JAMA Psychiatry, 70*(9), 931-939. doi:10.1001/jamapsychiatry.2013.1394

Dean, B. B., Gerner, D., & Gerner, R. H. (2004). A systematic review evaluating health-related quality of life, work impairment, and healthcare costs and utilization in bipolar disorder. *Current Medical Research and Opinion, 20*(2), 139-154. doi:10.1185/030079903125002801

Fazel, S., Zetterqvist, J., Larsson, H., Långström, N., & Lichtenstein, P. (2014). Antipsychotics, mood stabilisers, and risk of violent crime. *Lancet, 384*(9949), 1206-1214. doi:10.1016/S0140-6736(14)60379-2

Food and Health Bureau, H. K. S. A. R. (2017, April 18). Mental Health Review Report. Retrieved from https://www.fhb.gov.hk/download/press_and_publications/otherinfo/180500_mhr/e_mhr_full_report.pdf

Gao, L., Man, K. K. C., Chan, E. W., Chui, C. S. L., Li, X., Coghill, D., . . . Wong, I. C. K. (2021). Treatment with Methylphenidate for Attention Deficit Hyperactivity Disorder (ADHD) and the Risk of All-Cause Poisoning in Children and Adolescents: A Self-Controlled Case Series Study. *CNS Drugs, 35*(7), 769-779. doi:10.1007/s40263-021-00824-x

Hayes, J. F., Miles, J., Walters, K., King, M., & Osborn, D. P. (2015). A systematic review and meta-analysis of premature mortality in bipolar affective disorder. *Acta Psychiatrica Scandinavica, 131*(6), 417-425. doi:10.1111/acps.12408

Hayes, J. F., Pitman, A., Marston, L., Walters, K., Geddes, J. R., King, M., & Osborn, D. P. (2016). Self-harm, Unintentional Injury, and Suicide in Bipolar Disorder During Maintenance Mood Stabilizer Treatment: A UK Population-Based Electronic Health Records Study. *JAMA Psychiatry, 73*(6), 630-637. doi:10.1001/jamapsychiatry.2016.0432

Herrett, E., Thomas, S. L., Schoonen, W. M., Smeeth, L., & Hall, A. J. (2010). Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *British Journal of Clinical Pharmacology, 69*(1), 4-14. doi:10.1111/j.1365-2125.2009.03537.x

Hospital Authority. (2021). Introduction. Retrieved from https://www.ha.org.hk/visitor/ha_visitor_index.asp?Content_ID=10008&Lang=ENG&Dimension=100&Parent_ID=10004

Kishi, T., Ikuta, T., Matsuda, Y., Sakuma, K., Okuya, M., Mishima, K., & Iwata, N. (2021). Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: a systematic review and network meta-analysis of randomized controlled trials. *Molecular Psychiatry, 26*(8), 4146-4157. doi:10.1038/s41380-020-00946-6

Kishi, T., Matsuda, Y., Sakuma, K., Okuya, M., Mishima, K., & Iwata, N. (2020). Recurrence rates in stable bipolar disorder patients after drug discontinuation v. drug maintenance: a systematic review and meta-analysis. *Psychological Medicine*, 1-9. doi:10.1017/s0033291720003505

Lähteenvuo, M., Tanskanen, A., Taipale, H., Hoti, F., Vattulainen, P., Vieta, E., & Tiihonen, J. (2018). Real-world Effectiveness of Pharmacologic Treatments for the Prevention of

Rehospitalization in a Finnish Nationwide Cohort of Patients With Bipolar Disorder. *JAMA Psychiatry, 75*(4), 347-355. doi:10.1001/jamapsychiatry.2017.4711

Látalová, K. (2009). Bipolar disorder and aggression. *International Journal of Clinical Practice, 63*(6), 889-899. doi:10.1111/j.1742-1241.2009.02001.x

Legislative Council Secretariat. (2020, January 8). Updated background brief prepared by the Legislative Council Secretariat for the meeting on 10 January 2020. Retrieved from https://www.legco.gov.hk/yr19-20/english/panels/hs/papers/hs20200110cb2-468-4-e.pdf

Leung, G. M., Tin, K. Y., & O'Donnell, O. (2009). Redistribution or horizontal equity in Hong Kong's mixed public-private health system: a policy conundrum. *Health Economics, 18*(1), 37-54. doi:10.1002/hec.1342

Liao, Y. T., Ku, Y. H., Chen, H. M., Lu, M. L., Chen, K. J., Yang, Y. H., . . . Chen, V. C. (2021). Effect of medication on risk of traumatic brain injury in patients with bipolar disorder: A nationwide population-based cohort study. *Journal of Psychopharmacology, 35*(8), 962-970. doi:10.1177/02698811211013582

Malhi, G. S., Bell, E., Bassett, D., Boyce, P., Bryant, R., Hazell, P., . . . Murray, G. (2021). The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian and New Zealand Journal of Psychiatry, 55*(1), 7-117. doi:10.1177/0004867420979353

Man, K. K., Chan, E. W., Coghill, D., Douglas, I., Ip, P., Leung, L. P., . . . Wong, I. C. (2015). Methylphenidate and the risk of trauma. *Pediatrics, 135*(1), 40-48. doi:10.1542/peds.2014-1738

Man, K. K. C., Coghill, D., Chan, E. W., Lau, W. C. Y., Hollis, C., Liddle, E., . . . Wong, I. C. K. (2017). Association of Risk of Suicide Attempts With Methylphenidate Treatment. *JAMA Psychiatry, 74*(10), 1048-1055. doi:10.1001/jamapsychiatry.2017.2183

Man, K. K. C., Lau, W. C. Y., Coghill, D., Besag, F. M. C., Cross, J. H., Ip, P., & Wong, I. C. K. (2020). Association between methylphenidate treatment and risk of seizure: a population-based, self-controlled case-series study. *Lancet Child Adolesc Health, 4*(6), 435-443. doi:10.1016/s2352-4642(20)30100-0

McGinty, E. E., Baker, S. P., Steinwachs, D. M., & Daumit, G. (2013). Injury risk and severity in a sample of Maryland residents with serious mental illness. *Injury Prevention, 19*(1), 32-37. doi:10.1136/injuryprev-2011-040309

Miura, T., Noma, H., Furukawa, T. A., Mitsuyasu, H., Tanaka, S., Stockton, S., . . . Kanba, S. (2014). Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *Lancet Psychiatry, 1*(5), 351-359. doi:10.1016/s2215-0366(14)70314-1

Najt, P., Perez, J., Sanches, M., Peluso, M. A., Glahn, D., & Soares, J. C. (2007). Impulsivity and bipolar disorder. *European Neuropsychopharmacology, 17*(5), 313-320. doi:10.1016/j.euroneuro.2006.10.002

Ng, V. W. S., Man, K. K. C., Gao, L., Chan, E. W., Lee, E. H. M., Hayes, J. F., & Wong, I. C. K. (2021). Bipolar disorder prevalence and psychotropic medication utilisation in Hong Kong and the United Kingdom. *Pharmacoepidemiology and Drug Safety, 30*(11), 1588-1600. doi:10.1002/pds.5318

NICE. (2014, September 24). Bipolar disorder: assessment and management. Retrieved from https://www.nice.org.uk/guidance/cg185

Petersen, I., Douglas, I., & Whitaker, H. (2016). Self controlled case series methods: an alternative to standard epidemiological study designs. *British Medical Journal, 354*, i4515. doi:10.1136/bmj.i4515

Singhal, A., Ross, J., Seminog, O., Hawton, K., & Goldacre, M. J. (2014). Risk of self-harm and suicide in people with specific psychiatric and physical disorders: comparisons between disorders using English national record linkage. *Journal of the Royal Society of Medicine, 107*(5), 194-204. doi:10.1177/0141076814522033

Slankamenac, K., Heidelberger, R., & Keller, D. I. (2020). Prediction of Recurrent Emergency Department Visits in Patients With Mental Disorders. *Frontiers in Psychiatry, 11*, 48. doi:10.3389/fpsyt.2020.00048

Su, J. A., Cheng, B. H., Huang, Y. C., Lee, C. P., Yang, Y. H., Lu, M. L., . . . Chin-Hung Chen, V. (2017). Bipolar disorder and the risk of fracture: A nationwide population-based cohort study. *Journal of Affective Disorders, 218*, 246-252. doi:10.1016/j.jad.2017.04.037

Tang, W. N. (1997). Previous private psychiatric treatment among public mental patients: a preliminary local survey. *Hong Kong Medical Journal, 3*(3), 321-324.

Valtonen, H. M., Suominen, K., Haukka, J., Mantere, O., Leppämäki, S., Arvilommi, P., & Isometsä, E. T. (2008). Differences in incidence of suicide attempts during phases of bipolar I and II disorders. *Bipolar Disorders, 10*(5), 588-596. doi:10.1111/j.1399-5618.2007.00553.x

VanderWeele, T. J., & Ding, P. (2017). Sensitivity Analysis in Observational Research: Introducing the E-Value. *Annals of Internal Medicine, 167*(4), 268-274. doi:10.7326/m16-2607

Wang, Z., Chan, A. Y. L., Coghill, D., Ip, P., Lau, W. C. Y., Simonoff, E., . . . Man, K. K. C. (2021). Association Between Prenatal Exposure to Antipsychotics and Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, Preterm Birth, and Small for Gestational Age. *JAMA Internal Medicine, 181*(10), 1332-1340. doi:10.1001/jamainternmed.2021.4571

Weisler, R. H., Kalali, A. H., & Ketter, T. A. (2004). A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *The Journal of Clinical Psychiatry, 65*(4), 478-484. doi:10.4088/jcp.v65n0405

Whitaker, H. J., Hocine, M. N., & Farrington, C. P. (2009). The methodology of self-controlled case series studies. *Statistical Methods in Medical Research, 18*(1), 7-26. doi:10.1177/0962280208092342

Wong, A. Y., Wong, I. C., Chui, C. S., Lee, E. H., Chang, W. C., Chen, E. Y., . . . Chan, E. W. (2016). Association Between Acute Neuropsychiatric Events and Helicobacter pylori Therapy Containing Clarithromycin. *JAMA Internal Medicine, 176*(6), 828-834. doi:10.1001/jamainternmed.2016.1586

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., . . . Berk, M. (2018). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorders, 20*(2), 97-170. doi:10.1111/bdi.12609

Table 1. Characteristics of the study population

Characteristics	**All**	**Males**	**Females**
Patients receiving treatment of BPD, No. (%)	5040 (100)	1919 (38.08)	3121 (61.92)
Age at baseline, Mean (SD), years	38.10 (15.53)	37.64 (15.90)	38.39 (15.30)
Duration of follow-up, Mean (SD), years	16.32 (4.31)	15.91 (4.63)	16.57 (4.09)
Exposed period[a]			
No. of events	2367	860	1507
Total follow-up time, patient-years	44295.07	16241.12	28053.95
Unexposed period[b]			
No. of events	2673	1059	1614
Total follow-up time, patient-years	37959.51	14297.59	23661.92

[a] Exposed period refers to the time which the patient were treated with any of the pharmacological treatment agents of BPD (i.e. acute treatment and maintenance treatment)

[b] Unexposed period refers to the time which the patient were not treated with any of the pharmacological treatment agents of BPD (i.e. baseline, pre-exposure and post-exposure periods)

Abbreviations: BPD=bipolar disorder, SD=standard deviation

Table 2. Results from the self-controlled case series analyses

	No. of events	Patient- years	Crude incidence (per 100 patient-years)	Adjusted IRR[a] (95% CI)	P-value
Baseline	2443	36358.40	6.72	1.00	--
Pre-exposure period	133	370.32	35.91	4.44 (3.71-5.31)	<0.0001
Acute treatment	238	2603.05	9.14	1.44 (1.24-1.67)	<0.0001
Maintenance treatment	2129	41692.03	5.11	0.97 (0.88-1.06)	0.50
Post-exposure period	97	1230.79	7.88	1.34 (1.09-1.66)	0.006
Other medications adjusted (as time-varying confounders)					
Antidepressants during treatment	934	16187.31	5.77	1.08 (0.98-1.20)	0.1191
No antidepressants	4106	66067.27	6.21	1.00	--
Benzodiazepine derivatives during treatment	878	14845.54	5.91	1.29 (1.16-1.42)	<0.0001
No benzodiazepine derivatives	4162	67409.04	6.17	1.00	--
Direct comparison of maintenance treatment with pre-exposure period					
Pre-exposure period	133	370.32	35.91	1.00	--
Maintenance treatment	2129	41692.03	5.11	0.22 (0.18-0.26)	<0.0001
Direct comparison of maintenance treatment with acute treatment					
Acute treatment	238	2603.05	9.14	1.00	--
Maintenance treatment	2129	41692.03	5.11	0.67 (0.59-0.77)	<0.0001
Direct comparison of maintenance treatment with post-exposure period					
Post-exposure period	97	1230.79	7.88	1.00	--
Maintenance treatment	2129	41692.03	5.11	0.72 (0.58-0.89)	0.002

[a]All 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

Captions for figures

Figure 1. Graphical illustration of self-controlled case series study design: (a) overall use of any pharmacological agents, (b) stratifying by different drug classes

This figure shows the study design and timeline for a single hypothetical participant.

Figure 2. Flowchart of patient identification

This figure shows the selection criteria of patients included in the self-controlled case series analysis.

Figure 3. Results from the non-parametric spline based self-controlled case series analysis

This figure shows variation of incidence rate ratio (IRR) of emergency room admissions due to traumatic injuries between the time of pre/post exposure of treatment. The black solid line is the estimated IRR and the black dotted lines refer to its 95% confidence interval. The blue dotted line indicated baseline IRR.