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Association between the mood stabilizing treatment of bipolar disorder and risk of suicide attempts: A self-controlled case series study



Vanessa W.S. Ng , Miriam T.Y. Leung , Esther W. Chan ,
Edwin H.M. Lee , Joseph F Hayes , David P.J. Osborn ,
Yun Kwok Wing , Wallis C.Y. Lau , Kenneth K.C. Man ,
Ian C.K. Wong

PII: S0165-1781(23)00187-7
DOI: <https://doi.org/10.1016/j.psychres.2023.115236>
Reference: PSY 115236

To appear in: *Psychiatry Research*

Received date: 16 January 2023
Revised date: 21 April 2023
Accepted date: 3 May 2023

Please cite this article as: Vanessa W.S. Ng , Miriam T.Y. Leung , Esther W. Chan , Edwin H.M. Lee , Joseph F Hayes , David P.J. Osborn , Yun Kwok Wing , Wallis C.Y. Lau , Kenneth K.C. Man , Ian C.K. Wong , Association between the mood stabilizing treatment of bipolar disorder and risk of suicide attempts: A self-controlled case series study, *Psychiatry Research* (2023), doi: <https://doi.org/10.1016/j.psychres.2023.115236>

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Highlights

- Suicidality is a major public health concern and the rate of suicide attempts is high in patients with bipolar disorder.
- A key question is whether mood stabilizing treatment could lower the risk of suicide attempts.
- No causal association between use of mood stabilizing treatment and increased risk of suicide attempts.
- Lithium and antiepileptics were found to lower the risk of suicide attempts.
- Upon treatment discontinuation, the risk was elevated potentially due to symptoms relapse.

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Professor Ian C.K. Wong, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong, China (Tel: +852 3917 9441; email: wongick@hku.hk); Postal address: L2-57, Laboratory Block, 21 Sassoon Road, Pokfulam, Hong Kong

Dr. Kenneth K.C. Man, Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom (Tel: +44(0)2039872840; email: kenneth.man@ucl.ac.uk); Postal address: Mezzanine Floor, BMA House, Tavistock Square, London WC1H 9JP

Title: Association between the mood stabilizing treatment of bipolar disorder and risk of suicide attempts: A self-controlled case series study

Authors:

Vanessa W.S. Ng, BPharm^a, Miriam T.Y. Leung, MClinPharm^{a,b}, Esther W. Chan, PhD^{a,d,k,l},
Edwin H.M. Lee, MBChB^e, Joseph F Hayes, PhD^f, David P.J. Osborn, PhD^{f,g}, Yun Kwok Wing,
MBChB (Hons)^h, Wallis C.Y. Lau, PhD^{a,c,d,i}, Kenneth K.C. Man, PhD^{*a,c,d}, Ian C.K. Wong,
PhD^{*a,c,d,j}

Affiliations:

^a Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy,
The University of Hong Kong, Hong Kong, China

^b Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences,
Monash University, Melbourne, Victoria, Australia

^c Research Department of Practice and Policy, School of Pharmacy, University College London,
London, United Kingdom

^d Laboratory of Data Discovery for Health (D²4H), Hong Kong Science Park, Hong Kong, China

^e Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong,
Hong Kong, China

^f Division of Psychiatry, Faculty of Brain Sciences, University College London, London, United
Kingdom

^g Camden and Islington NHS Foundation Trust. London NW10PE

^h Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China.

ⁱ Centre for Medicines Optimisation Research and Education, University College London Hospitals NHS Foundation Trust, London, UK.

^j Aston Pharmacy School, Aston University, Birmingham, United Kingdom

^k Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

^l The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China

Abstract (words: 200)

Bipolar disorder (BPD) is associated with high rates of suicide attempts but the anti-suicidal effect of mood stabilizing agents remains unclear. This study aimed to examine the association between mood stabilizing agents (lithium, valproate, lamotrigine, carbamazepine or antipsychotics) and risk of suicide attempts in patients with BPD using self-controlled case series study design.

Among 14087 patients with BPD who received mood stabilizing agents from 2001-2020 in Hong Kong, 1316 patients had at least one suicide attempts during the observation period. An increased risk of suicide attempts was observed 14 days before treatment initiation compared to non-exposed period. Following treatment initiation, an increased risk with smaller magnitude was found with the use of mood stabilizing agents. A lower risk was observed with lithium and antiepileptics while the risk remained attenuated with decreasing magnitude with antipsychotics. During 30-day post-treatment period, the risk was elevated. Therefore, this study suggests that use of mood stabilizing agents is not causally associated with an increased risk of suicide attempts. Indeed, there are potential protective effects of lithium and antiepileptics against suicide attempts. Assiduous monitoring of symptoms relapse and warning signs of suicide should be part of the management plan and discussed between clinicians, caregivers and patients.

Keywords

Lithium; antipsychotics; antiepileptics; within-individual comparison; electronic health records

Manuscript (words: 4073)**1. Introduction**

Suicidality is a major public health concern and the rate of suicide attempts is high in patients with bipolar disorder (BPD). Patients with BPD are at least 10 times more likely to attempt suicide than the general population and more than twice as likely as patients with major depression (Chen and Dilsaver, 1996; Sher, 2008). Whilst suicide is one of the major causes of premature death among patients with BPD, suicidality has far-reaching adverse impacts on the individual, their families, peers, and society (Hayes et al., 2015). Therefore, suicide prevention remains one of the priority global targets in the Mental Health Action Plan 2013-2030 by World Health Organization (World Health Organization Mental Health and Substance Use, 2021).

Pharmacological treatment is recommended to patients with BPD. A growing body of research has been conducted on the effect of mood stabilizing treatment on suicide attempts among patients with BPD. Lithium is recommended as a first-line treatment of BPD by international clinical guidelines because of its profound efficacy in relieving mood fluctuation and relapse prevention (Malhi et al., 2021; NICE, 2014; Yatham et al., 2018). In recent decades, lithium use has greatly declined and been replaced by other alternatives, such as antipsychotics and mood stabilizing antiepileptics (valproate, carbamazepine, lamotrigine) (Bjørklund et al., 2016; Lin et al., 2020; Ng et al., 2021). Lithium has been suggested to have anti-suicidal effects and accumulated studies demonstrated a protective effect of lithium on suicidality (Cipriani et al., 2013; Wilkinson et al., 2022). However, an updated meta-analysis which only included randomized controlled trials (RCTs) from year 2000 onwards reported no significant differences in suicidal behavior, including suicides and suicide attempts between lithium and placebo groups (Nabi et al., 2022). In 2008, U.S Food and Drug Administration (FDA) issued a warning about

the increased risk of suicide with the use of antiepileptics, but subsequent studies were unable to confirm this finding due to conflicting evidence (Antolín-Concha et al., 2020; Ferrer et al., 2014; Leon et al., 2012; Patorno et al., 2010; Tsai et al., 2016). The effect of antipsychotics on the risk of suicide attempts among patients with BPD is yet sparsely investigated. Previous studies reported that antipsychotics is associated with an increased risk of suicide, while some studies have shown that atypical antipsychotics may lower the risk (Koek et al., 2012; Pompili et al., 2016).

Yet, accumulated studies have showed that the mood stabilizers (including lithium and mood stabilizing antiepileptics) may improve not only the suicidal behavior but also the physical health of patients with BPD. Lithium and valproate were found to be associated with decreased risk of natural mortality due to various physical diseases (Chen et al., 2023). However, the use of antipsychotics, which have been recommended as one of the treatment options for BPD, was reported to have great potential to adversely affect the physical health and a prior study found an increased risk of cardiovascular mortality associated with antipsychotics (Correll et al., 2015; Lin et al., 2023). Therefore, it has been unclear whether the overall use of pharmacological treatment of BPD could reduce the risk of suicide attempts as the three classes of mood stabilizing agents with their respective underlying mechanisms of actions might have different effects on the course of illness and physical health, which might indirectly affect the risk the suicide attempts. Although the effectiveness of various treatment regimen on mood stabilization has been recognized, the occurrence of adverse effects also plays a role in affecting the risk of suicide attempts. We hypothesized that use of mood stabilizing agents would not increase the risk of suicide attempts among patients with BPD and that different classes of mood stabilizing agents

would exhibit different associations with suicide attempts owing to their varying effects on mood symptoms and physiological functions.

There are some common limitations in RCTs and observational studies that might affect the findings, such as limited sample size and follow-up periods. In the existing literature, most of the observational studies on the suicidal behavior associated with psychotropic medications applied the study design of between-individual comparison, such as cohort study design (Gibbons et al., 2009; Hayes et al., 2016; Smith et al., 2009). “Between-individual comparison” refers to the comparison between different individuals with similar characteristics in the comparator and control groups, where the comparator group indicates the presence of exposure or outcome of interest and control group indicates their absence, depending on which study designs chosen (Lao et al., 2016). Most of between-individual comparison studies might not be able to identify the time-varying risk patterns when patients switched or received additional medications and more importantly, are highly susceptible to confounding by indication as patients are prescribed a particular medication based on their risks of outcomes (Gibbons et al., 2009; Hayes et al., 2016; Smith et al., 2009). Furthermore, many time-invariant factors that might confound the risk of suicide attempts were not measured in prior studies (e.g. family history of suicide, genetic makeup) (Hayes et al., 2016; Smith et al., 2009). Therefore, to tackle these methodological limitations from between-individual comparison designs, we applied a self-controlled case series (SCCS) study design, which enables comparison within the same individual and thus implicitly controls the time-invariant confounders (Whitaker et al., 2009), to investigate the association between the mood stabilizing agents and the risk of suicide attempts.

2. Method

2.1 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 a sole publicly-funded healthcare services provider offering medical and ambulatory services available to all Hong Kong residents (>7.4 million) (Hospital Authority, 2021). The clinical data from each individual who has ever utilized public healthcare services in Hong Kong, including medical diagnoses recorded at different settings (inpatient, general and specialist outpatient clinics, psychiatric inpatient and outpatient clinical services), medication dispensing records, accidents and emergency attendances, hospital admissions and discharges records, psychiatric outpatient and inpatients attendance records, as well as all other general and specialist outpatients attendance records, have been continuously updated for research and audit purposes. The medical diagnoses are usually made by clinicians, including psychiatrists, particularly for mental disorders. CDARS does not capture clinical data from the private healthcare sectors but a local study reported that approximately 88.5% of psychiatric patients utilized public mental health services under HA (Tang, 1997). Therefore, 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 on medication safety (Man et al., 2017; Ng et al., 2021). There is no patient interaction involved in this study and hence written informed consent was waived. The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW19-409).

2.2 Study Design

We investigated the association between the mood stabilizing agents of BPD and suicide attempts using a SCCS design, which enables intrapersonal comparison in patients with both

exposure and outcome of interests during the observation period. Each patient serves as their own control and this study design inherently controls for measured and unmeasured time-invariant confounding factors (Whitaker et al., 2009).

2.3 Case Identification

The study population comprised of patients diagnosed with BPD (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 296.0, 296.1, and 296.4-296.8) from database inception (i.e. 1st January 1993) to 31st December 2019. Patients were included if they were aged 18 years or above, as BPD is rarely diagnosed in children and adolescents (NICE, 2014). Patients with a diagnosis of schizophrenia or schizoaffective disorder (ICD-9-CM: 295) after the diagnosis of BPD were excluded. Cases were defined as patients with BPD who had received at least one prescription of mood stabilizing agents (lithium, valproate, lamotrigine, carbamazepine or antipsychotics) and at least one record of suicide attempt (ICD-9-CM: E950-E959) within the observation period. Patients with prior history of suicide attempts before the observation period were excluded. The individual observation period commenced 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 2020 or the date of registered death (whichever was earlier).

2.4 Exposures and Outcomes

We identified all prescriptions of the mood stabilizing agents and suicide attempts among patients with BPD. These medications are commonly used as treatment of BPD in Hong Kong (Ng et al., 2021). We defined exposure periods as the duration between the prescription start and end dates of each prescription recorded on CDARS. Less than 0.2% of the prescriptions have

missing prescription start and end dates. If the prescription start date was not available, the dispensing date was used. For those prescriptions with missing prescription end dates, the treatment duration was calculated using daily dosages and quantity prescribed. We imputed the median duration of different drug classes for those prescriptions when any of the above information was incomplete.

The observation period of each individual was divided into four discrete windows: 1) absence of all treatment (baseline period), 2) 14 days before each exposure to treatment (pre-exposure period), 3) use of mood stabilizing agents, and 4) 30 days after the end of exposure of treatment (post-exposure period). A pictorial representation of the observation timeline of a single hypothetical participant is illustrated in Figure 1A. A pre-exposure period was added to take account of any effects of suicide attempts, which might alter the likelihood of initiating the treatment and potentially bias the risk estimates during the treatment.

2.5 Statistical Analysis

2.5.1 Primary analysis: all mood stabilizing agents as a composite exposure

Incidence rate ratios (IRRs) with 95% confidence intervals (CI) were estimated by comparing the incidence rates of suicide attempt during different windows using conditional Poisson regression. 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 stratified by sex.

2.5.2 Secondary analysis: Stratifying by three study drug classes (i.e. lithium, antipsychotics, antiepileptics)

When stratifying the exposure of interest by three different drug classes (lithium, antipsychotics, mood stabilizing antiepileptics), the designated risk periods were dedicated specifically to each drug class (Fig. 1B). While one of the drug classes became the exposure of interest (i.e. study drug class), the concurrent use of the remaining two drug classes were adjusted as time-varying confounders. Patients who attempted suicide with exposure to at least one of the study drug classes were included in the analysis as not all patients received all three drug classes of mood stabilizing agents throughout the observation period. This could also lead to a better adjustment for time-varying confounders on the risk of suicide attempts (Ghebremichael-Weldeslassie et al., 2022; Whitaker et al., 2009). Further analysis was conducted by removing unexposed cases to validate this approach. Similar to the primary analysis, in addition to the concurrent use of mood stabilizing agents other than study drug class, time-varying confounders, such as age in 1-year band and concurrent use of antidepressants and/or benzodiazepines, were also adjusted. IRR and 95% CIs were estimated by comparing the incidence rates of suicide attempts in different risk windows with the baseline periods with respect to the study drug class only using conditional Poisson regression.

2.5.3 Sensitivity analyses

To examine the robustness of our results, we conducted several sensitivity analyses with different definitions of study cohort, criteria of defining observation period, and lengths of exposure period, including removing all patients who died during the observation period and within 30 days after the first suicide attempts respectively; removing patients with schizophrenia; restricting the study cohort to new users of mood stabilizing treatment; removing individuals who had suicide attempts on the first day of any mood stabilizing agents; removing patients with substance abuse; 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; restricting the observation period to 31st December 2019 to remove the effect of COVID-19 pandemic on the results and different drug non-adherence scenarios. To account for any potential residual confounding, we conducted an E-value analysis to quantify the likelihood of time-varying residual confoundings that would nullify the observed association (VanderWeele and Ding, 2017). A previous study reported that hypnotics and anxiolytics would increase the risk of suicide ideation, so we further adjusted for concurrent use of hypnotics and anxiolytics as a time-varying confounder (Lecat et al., 2020). We also redefined the pre-exposure period as 30, 60 and 90 days and the post-exposure period as 14, 60 and 90 days to test the adequacy of a 14-day pre-exposure period and a 30-day post-exposure period in the primary and secondary analyses. Details of sensitivity analyses were shown in Supplementary Table 1. A significance level of 5% was used in all statistical analyses. Data manipulation and analysis were conducted using SAS (version 9.4) and R (version 3.5.3; R Core Team).

3. Results

Between 1st January 2001 and 31st December 2020, 1316 adult patients with BPD who prescribed any mood stabilizing agents and attempted suicide at least once within the observation period were included in the analysis (Fig. 2). Of these, antipsychotics prescribing was the most prevalent, followed by antiepileptics and lithium respectively. Among 1276 patients who ever received antipsychotics during the observation period, the most commonly prescribed antipsychotic was quetiapine (69.9%), followed by haloperidol (64.3%) and olanzapine (38.2%). Details of the characteristics of patients included in the analysis were shown in Table 1.

The analysis indicated an association between use of mood stabilizing agents and risk of suicide attempts (Table 2). Overall, an increased risk was observed during the 14-day pre-exposure period (IRR=36.95, 95% CI 30.02-45.47). The risk was attenuated with smaller magnitudes after treatment initiation (IRR=2.36, 95% CI 1.95-2.85). IRR increased during the post-exposure period (IRR=5.03, 95% CI 3.70-6.84). When stratifying by different drug classes (Table 3), the risk of suicide attempt was significantly elevated during the pre-exposure period for all drug classes compared to their own baseline periods (lithium: IRR=3.15, 95% CI 2.05-4.84; antipsychotics: IRR=16.47, 95% CI 12.86-21.10; antiepileptics: IRR=6.03, 95% CI 4.61-7.89). A decreased risk was observed with the use of lithium (IRR=0.57, 95% CI 0.43-0.75) and antiepileptics (IRR=0.79, 95% CI 0.65-0.95) respectively while an increased risk with decreasing magnitude was detected with the use of antipsychotics (IRR=2.70, 95% CI 2.24-3.26) relative to its baseline. There was an increased risk in both post-lithium (IRR=1.96, 95% CI 1.13-3.40) and post-antipsychotic (IRR=4.79, 95% CI 3.52-6.53) periods while the risk returned to baseline in post-antiepileptic periods (IRR=0.74, 95% CI 0.43-1.28).

Further analysis using non-parametric spline-based SCCS showed that the risk of suicide attempts started to rise and reached the peak within 10 days before treatment initiation and then dropped to the baseline within around 30 days after treatment initiation (Supplementary Figure 1). Similar effects were observed in the sex-stratified analysis (Supplementary Table 2). A total of 166 patients died within the observation period, in which 21 patients died within 30 days after their first suicide attempts (Supplementary Figure 2). The results from the sensitivity analyses were generally consistent with the main analysis (Supplementary Table 3 and Supplementary Figures 3-5). After removing the unexposed patients to the study medications, the results were similar but with a larger magnitude in terms of IRR (Supplementary Table 3). The results of E-value analysis was summarized in Supplementary Table 4.

4. Discussion

In this study, we found an increased risk of suicide attempts with decreasing magnitudes associated with the use of mood stabilizing agents. When stratifying by different drug classes, lithium and antiepileptics were associated with a lower risk while a positive association was observed with antipsychotics. The 14-day pre-exposure period showed a high incidence of suicide attempts of all mood stabilizing agents, implicating that patients might already have developed worsening symptoms or suicide ideation, which lead to treatment initiation. An increased risk was observed during the period which the use of lithium and antipsychotics were intermittently ceased compared to baseline periods. This conclusion remained robust throughout the sensitivity analyses.

There has been an ongoing discussion on the potential anti-suicidal effect of the mood stabilizing agents. A meta-analysis of RCTs and observational studies on lithium reported a pooled estimate of 0.46 (95% CI 0.40-0.85) relative to the placebo (Wilkinson et al., 2022), which is consistent

with our findings. However, the evidence from another updated meta-analysis which included RCTs after the year 2000 only on the anti-suicidal effect of lithium compared to placebo was inconclusive (Nabi et al., 2022). Several factors might explain the discrepancy of the findings. Firstly, more than half of the trials had zero events in both lithium and placebo groups. Secondly, the sample size in the trials were small (most were <100). Thirdly, the follow-up time of most of the trials were less than 1 year, and lastly most of trials were conducted in Caucasian population. Our findings on the protective effect of lithium on suicide attempts will hopefully contribute to the literature and further studies in different population will be warranted to enhance the generalizability.

Antipsychotics are often used in monotherapy or combination treatment for BPD. Our study reported that an increased risk of suicide attempts associated with the use of antipsychotics relative to baseline periods, but with a smaller magnitude compared to its pre-exposure period. Antipsychotics has been evident in relieving neuropsychiatric symptoms, which might potentially lower the risk (Kishi et al., 2020). However, the adverse effects of antipsychotics (e.g. extrapyramidal side effects, and metabolic syndrome), the natural course of BPD could also be the factors that potentially increase the likelihood of suicide attempts. Another possibility is that there has been an increasing trend of using antipsychotics as a method of suicide (Mainio et al., 2021). The complex interplay of the association between each contributing factor makes it difficult to identify the actual reason for the overall increased risk. The higher risk might not be attributable to antipsychotics alone. Therefore, the result should be interpreted cautiously.

After the U.S FDA issued a warning on the potential increased suicidality with the use of antiepileptics, many clinical trials and observational studies have been conducted to validate this finding. Yet, no clear evidence was available in patients with BPD. Prior studies showed no

increased risk of suicide attempts with the use of antiepileptics in patients with BPD (Gibbons et al., 2009; Leon et al., 2012). In our study, a decreased risk was observed with the use of antiepileptics relative to baseline intervals. However, when we removed unexposed patients to antiepileptics in one of the sensitivity analysis, no association was observed with antiepileptics during the treatment period, possibly due to small sample size. Therefore, further studies will be warranted to confirm this association.

Although the inherent mechanisms leading to suicidal behavior has been complex and remaining elucidated, current evidence to date suggested mood instability and uncontrolled aggression and impulsivity are the potential risk factors of suicide attempts related to the illness of BPD (Kulacaoglu and Izci, 2022; Palmier-Claus et al., 2012). Our study showed that the risk of suicide attempts was attenuated with a decreasing magnitude following the treatment initiation, implicating the ability of mood stabilizing agents on mood stabilization, which reduces the likelihood of suicide attempts. Specifically, previous studies demonstrated lithium's anti-suicidal effect potentially via reducing aggression and impulsivity in addition to mood stabilization (Cipriani et al., 2013; Wilkinson et al., 2022). An increased risk was observed during the period which mood stabilizing agents were ceased/with-held. Such increase during the post-exposure period might be potentially due to symptoms relapse or withdrawal effects which may induce suicide ideation in patients. Therefore, close monitoring of patients' symptoms and warning signs of suicide is essential, especially when clinicians and/or patients decide to discontinue or temporarily with-hold treatment.

One of the major strengths is the use of a population-based electronic health record database in this study. CDARS provides sufficiently large statistical power to evaluate the association between the use of different mood stabilizing agents and the risk of suicide attempts. The

strength of using a SCCS study design is to eliminate all time-invariant confounders. The risk factors for suicide behavior are deemed to be multifactorial, which could be potential confounders but unavailable in CDARS, such as genetic and familial predisposition to suicide, adverse childhood experiences, financial distress and other environmental factors. Those risk factors at baseline are implicitly controlled to prevent bias to the result estimates. For the validity of the clinical data, the HA manages the majority of patients who need specialist care in Hong Kong (Leung et al., 2005). Patients with BPD were managed by the specialists at the hospitals and their diagnosis were confirmed for further clinical management. 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 et al., 2010).

There are limitations to be acknowledged. Firstly, 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 clinicians at private sector but patients with BPD usually require lifelong treatment and would often prefer public services due to subsidized medical costs (Leung et al., 2009). Therefore, our study likely covered most of the patients with BPD in Hong Kong. Furthermore, like other observational studies using electronic databases, CDARS only provides information relating to medication dispensing records but adherence to treatment cannot be measured. 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. We addressed this by extending the exposure periods from 1-10 weeks in our sensitivity analysis and results remained consistent with the main analysis. Secondly, the

incidence of suicide attempts could be under-reported since the suicide attempters with minor injuries might not seek medical attention under the pressure of social stigma. Thirdly, the cause of death of patients who died by suicide were not well-recorded in CDARS as those died by suicides were not validated by Coroner's court in Hong Kong so we would not be able to capture patients who died by suicide. However, the outcome of this study was suicide attempts so death by suicide is only of secondary interest. Finally, the follow-up period in our study was relatively long that some residual time-varying confounders might appear over time and potentially affect our result. Although we already measured the E-value to estimate the effect of residual confounders which would nullify the observed association, we could not eliminate the possibility of residual confounding by just referring to E-value. One of the time-varying residual confounders, which is presumed to have an impact on risk of suicide attempts, is the occurrence of mood symptoms. Patients with BPD have mood fluctuations during the course of illness, which might potentially confound the observed association. It is challenging to examine the mood symptoms that patients developed during the observation period. In Hong Kong, clinicians only record the diagnosis of BPD using ICD-9-CM codes in CDARS once the diagnosis is confirmed and the changes or occurrence of mood symptoms could not be identified using ICD-9-CM codes. However, we adjusted for the concurrent use of psychotropic medications, which can be used as a proxy to indicate the occurrence of mood symptoms, in the main and sensitivity analyses. The results of both main and sensitivity analyses remained consistent.

In conclusion, our findings do not support a causal relationship between the use of mood stabilizing agents and increased risk of suicide attempts. A high incidence was observed before start of the treatment. Following treatment initiation, an increased risk with decreasing magnitude was found with the overall use of mood stabilizing agents. Lithium and antiepileptics

were associated with lower risk relative to the baseline periods, implicating anti-suicidal potential. The risk was attenuated during the use of antipsychotics, despite a much smaller magnitude detected compared to the pre-exposure period. An increased risk with higher magnitude relative to the treatment period was observed when mood stabilizing agents were with-held. Clinicians and caregivers should be mindful of potential relapse of mood episodes, signs of suicide ideation, particularly when discontinuing or temporarily with-holding treatment.

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Acknowledgments: We thank the Hong Kong Hospital Authority for granting access to the data from CDARS for research purposes.

Funding: This work was supported by AIR@InnoHK administered by Innovation and Technology Commission of the Hong Kong SAR Government.

Financial support: Vanessa W.S. Ng is supported by the Postgraduate Student Scholarship from The University of Hong Kong. Miriam T.Y. Leung is supported by Australian Government Research Training Program Scholarship. Joseph F Hayes is supported by UKRI grant MR/V023373/1, the University College London Hospitals NIHR Biomedical Research Centre and the NIHR North Thames Applied Research Collaboration. David P.J. Osborn is supported by the University College London Hospitals NIHR Biomedical Research Centre and the NIHR North Thames Applied Research Collaboration. Other authors received no specific funding for this work. The funder had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The views expressed in this article are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

Conflict of interest: Esther W Chan has received grants from Research Grants Council (RGC, Hong Kong), Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Novartis, Amgen, AstraZeneca, Takeda, the RGA Reinsurance Company, Narcotics Division of the Security Bureau of the Hong Kong Special Administrative Region, the National Health and Medical Research Council Australia; consulting fees from AstraZeneca, Pfizer and Novartis; and honorarium from the Hospital Authority Hong Kong, outside the submitted work. Joseph F

Hayes has received consultancy fees from Wellcome Trust and Juli Health. Yun Kwok Wing has received honorarium from Eisai Hong Kong and consultation fees from Eisai Co., Ltd, grants from Research Grants Council (RGC, Hong Kong). Wallis C.Y. Lau reports grant from AIR@InnoHK administered by Innovation and Technology Commission, outside the submitted work. Kenneth K.C. Man received the CW Maplethorpe Fellowship, grants from the National Institute for Health Research, United Kingdom; the European Union Horizon 2020 Framework; Hong Kong Research Grant Council and personal fees from IQVIA Holdings, Inc., unrelated to this work. Ian C.K. Wong has received grants from the Research Grants Council (RGC, Hong Kong), the National Institute for Health Research, United Kingdom, National Health and Medical Research Council in Australia, Innovative Medicines Initiative (IMI), Shire, Janssen-Cilag, Eli-Lily, Pfizer, Bayer, Bristol-Myers Squibb, Takeda, Amgen, AstraZeneca and the European Union FP7 program. He is a member of the National Institute for Health and Clinical Excellence (NICE) ADHD Guideline Group, the British Association for Psychopharmacology ADHD guideline group and an advisor to Shire. He also receives personal fee from IQVIA and Jacobson Pharmaceutical and speaker fees from Janssen and Medice in the previous 3 years. Vanessa W.S. Ng, Miriam T.Y. Leung, Edwin H.M. Lee, and David P.J. Osborn, declare no conflict of interest.

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Table 1. Patient characteristics

Characteristics	All (n=1316)	Lithium[#] (n=457)	Antipsychotics[#] (n=1276)	Antiepileptics[#] (n=1015)
Male (%)	486 (36.93)	169 (36.98)	474 (37.15)	368 (36.26)
Age at baseline, Mean (SD), years	32.44 (12.62)	31.73 (11.76)	32.49 (12.58)	32.61 (12.60)
Duration of follow-up, Mean (SD), years	16.69 (4.91)	17.04 (4.54)	16.74 (4.90)	17.05 (4.57)
Exposed period				
No. of events	717	99	618	367
Total follow-up time, patient-years	11262.85	2153.06	9385.11	6909.16
Unexposed period				
No. of events	599	358	658	648
Total follow-up time, patient-years	10700.90	5633.19	11968.88	10397.83

[#]1052 patients were treated with >1 drug class during the observation period so the number of patients who were treated with different drug classes did not sum up to the total number of patients included in the analysis.

Abbreviations: SD=standard deviation

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

Risk periods	No. of events	Patient years	Crude incidence (per 100 patient-years)	Adjusted IRR^a (95% CI)	<i>p</i>-value
All mood stabilizing agents (n=1316)					
Baseline	397	10131.55	3.92	1.00	--
Pre-exposure period	151	135.68	111.29	36.95 (30.02-45.47)	<.001
Exposure period	717	11262.85	6.37	2.36 (1.95-2.85)	<.001
Post-exposure period	51	433.68	11.76	5.03 (3.70-6.84)	<.001
Other medications adjusted (as time-varying factor)					
Antidepressants during treatment	486	5952.12	8.17	1.77 (1.50-2.10)	<.001
No antidepressants	830	16011.63	5.18	1.00	--
Benzodiazepine derivatives during treatment	478	5316.54	8.99	2.54 (2.16-2.99)	<.001
No benzodiazepine derivatives	838	16647.21	5.03	1.00	--

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

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

Table 3. Results from the self-controlled case series analyses stratified by different drug classes

Risk periods	No. of events	Patient years	Crude incidence (per 100 patient-years)	Adjusted IRR ^a (95% CI)	p-value
Lithium					
Baseline ^b	1171	19697.66	5.94	1.00	--
Pre-exposure period	31	28.61	108.35	3.15 (2.05-4.84)	<.001
Exposure period	99	2153.06	4.60	0.57 (0.43-0.75)	<.001
Post-exposure period	15	84.42	17.77	1.96 (1.13-3.40)	.02
Antipsychotics					
Baseline ^b	499	12017.68	4.15	1.00	--
Pre-exposure period	142	138.89	102.24	16.47 (12.86-21.10)	<.001
Exposure period	618	9385.11	6.58	2.70 (2.24-3.26)	<.001
Post-exposure period	57	422.07	13.50	4.79 (3.52-6.53)	<.001
Antiepileptics (i.e. valproate, carbamazepine and lamotrigine)					
Baseline ^b	833	14705.42	5.66	1.00	--
Pre-exposure period	101	83.75	120.60	6.03 (4.61-7.89)	<.001
Exposure period	367	6909.16	5.31	0.79 (0.65-0.95)	.01
Post-exposure period	15	265.43	5.65	0.74 (0.43-1.28)	.28
Other medications adjusted (as time-varying factor)					
Antidepressants during treatment	486	5952.12	8.17	1.87 (1.58-2.21)	<.001
No antidepressants	830	16011.63	5.18	1.00	--
Benzodiazepine derivatives during treatment	478	5316.54	8.99	2.57 (2.18-3.02)	<.001
No benzodiazepine derivatives	838	16647.21	5.03	1.00	--

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

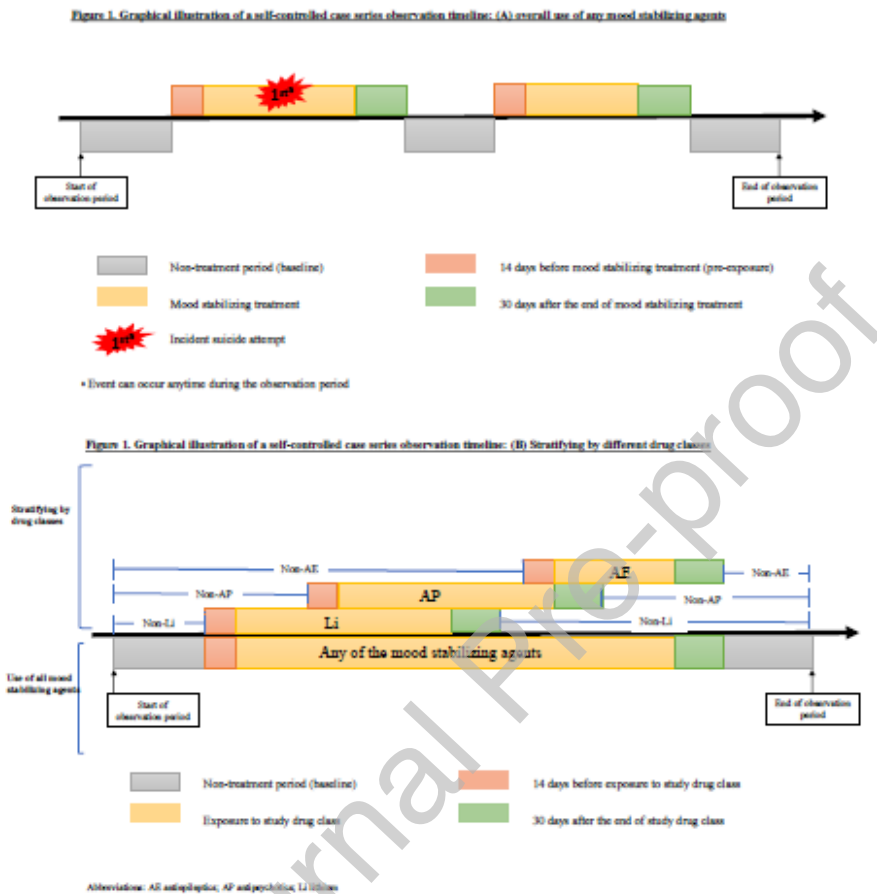
^bWhen stratifying by drug classes, baseline period refers to remaining periods (other than pre-exposure, exposure and post-exposure periods) to study drug class.

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

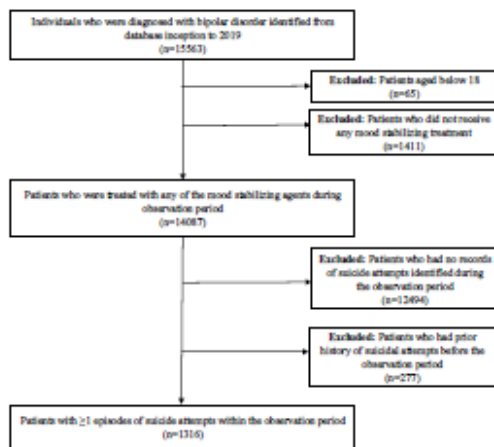
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Figure legends

Figure 1. Graphical illustration of a self-controlled case series observation timeline: (A) overall use of any mood stabilizing agents, (B) stratifying by different drug classes



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

Figure 2. Flowchart of patients included

This figure reports the number of patients included at each stage based on the selection criteria.

CRediT Author Statement

Vanessa W.S. Ng: Conceptualization, Software, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project administration

Miriam T.Y. Leung: Validation, Formal analysis, Writing - Review & Editing

Esther W. Chan: Writing - Review & Editing

Edwin H.M. Lee: Writing - Review & Editing

Joseph F Hayes: Writing - Review & Editing

David P.J. Osborn: Writing - Review & Editing

Yun Kwok Wing: Writing - Review & Editing

Wallis C.Y. Lau: Writing - Review & Editing

Kenneth K.C. Man: Conceptualization, Writing - Review & Editing, Supervision

Ian C.K. Wong: Conceptualization, Resources, Writing - Review & Editing, Supervision, Funding acquisition