Original Investigation

Association Between Acute Neuropsychiatric Events and *Helicobacter pylori* Therapy Containing Clarithromycin

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IMPORTANCE There is a concern that *Helicobacter pylori* therapy containing clarithromycin might be associated with acute neuropsychiatric events.

OBJECTIVE To examine the association between *H pylori* therapy containing clarithromycin and acute neuropsychiatric events.

DESIGN, SETTING, AND PARTICIPANTS A self-controlled case series study was conducted using the Clinical Data Analysis and Reporting System database in Hong Kong to explore any association. The exposure of interest was *H pylori* therapy containing clarithromycin in the outpatient setting. Study patients, 18 years or older at cohort entry, must have had both exposure to *H pylori* therapy containing clarithromycin and their first recorded neuropsychiatric events between January 1, 2003, and December 31, 2012. A post hoc nested case-control analysis was also performed in patients receiving *H pylori* therapy containing clarithromycin.

MAIN OUTCOMES AND MEASURES The primary outcome was composite neuropsychiatric events, while secondary outcomes were psychotic events and cognitive impairment. Risk periods in the self-controlled case series analysis were defined as 14-day preexposure period, current use (days 1-14 since prescription start date) and recent use (days 15-30). Age-adjusted incidence rate ratios (IRR) were estimated using the conditional Poisson regression.

RESULTS Of 66 559 patients who had at least 1 outpatient prescription of *H pylori* therapy containing clarithromycin. Their mean (SD) age at cohort entry was 50.8 (14.8 years); their mean age at first exposure was 55.4 (14.8) years, and 30 910 were male (46.4%). A total of 1824 patients had their first recorded composite neuropsychiatric events during the study period. An increased IRR of 4.12 (35 composite neuropsychiatric events during 72 person-years; 95% CI, 2.94-5.76) during current use was observed but not in recent use (9 events during 82 person-years; IRR, 0.95; 95% CI, 0.49-1.83) and 14-day preexposure period (14 events during 72 person-years; IRR, 1.63; 95% CI, 0.96-2.77) vs baseline (1766 events during 16 665 person-years). Similarly, both the risk of psychotic events and cognitive impairment increased during current use vs baseline, although this subsequently returned to baseline incidence levels during recent use. The crude absolute risks of composite neuropsychiatric events, psychotic events, and cognitive impairment during current use were 0.45, 0.12, and 0.12 per 1000 prescriptions, respectively. The nested case-control analysis also gave similar results to that of the self-controlled case series analysis.

CONCLUSIONS AND RELEVANCE This study shows evidence of a short-term increased risk of neuropsychiatric events associated with *H pylori* therapy containing clarithromycin.

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Clarithromycin is used for the treatment of respiratory infections, including community-acquired pneumonia.[1] It is also commonly prescribed in combination with amoxicillin or metronidazole, plus proton pump inhibitors (PPIs) as a first-line standard treatment for *Helicobacter pylori eradication*.[2] Among potential adverse events associated with the use of clarithromycin, neuropsychiatric symptoms were described in 1995 when 2 patients with AIDS developed delusions, anxiety, and agitation following treatment with clarithromycin for *Mycobacterium avium* complex infection.[3] Thereafter, several case reports raised concerns that clarithromycin might be associated with neuropsychiatric events in patients with or without other long-term comorbidities, such as renal disease, hypertension, and obstructive airway disease.[4-16] One literature review reported 38 adult patients with clarithromycin-induced neuropsychiatric events also suggesting a possible link between clarithromycin and neuropsychiatric events.[17] Most of the reported neuropsychiatric symptoms were related to psychotic manifestations and cognitive disturbances.[17] In these reports, the neuropsychiatric symptoms seemed to be resolved after discontinuation of clarithromycin treatment. Notably, clarithromycin was frequently reported to be associated with mania based on unpublished reports from the World Health Organization and the US Food and Drug Administration.[18]

Apart from clarithromycin monotherapy, neuropsychiatric symptoms were also observed in patients receiving *H pylori* therapy containing clarithromycin.[19-25] Despite signal detection implicating clarithromycin as the causative agent of neuropsychiatric events, to our knowledge, no population-based study has been conducted to assess and evaluate the neuropsychiatric risk associated with clarithromycin.

Patients receiving clarithromycin might have a higher risk of severe acute infections than those prescribed amoxicillin or other penicillins. Owing to different underlying neuropsychiatric risks, indication bias might result in findings of noncausal associations. In our previous work, we examined the association between cardiovascular events and clarithromycin using the cohort of *H pylori* therapy containing clarithromycin in a secondary analysis to reduce confounding.[26] Using similar methods, we further explored the safety considerations of clarithromycin in this study by investigating the association between *H pylori* therapy containing clarithromycin and acute neuropsychiatric events.

Methods

Data Sources

The study protocol was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. The data were retrieved from the Clinical Data Analysis and Reporting System database, which is developed and managed by the Hospital Authority in Hong Kong.[27] The Hospital Authority currently manages 42 public hospitals and institutions, 47 specialist outpatient clinics, and 73 general outpatient clinics.[28] More than 7 million local residents have access to these primary, secondary, and tertiary public health care services through 7 hospital clusters.[27] In the Hos-

Key Points

Question Is there an association between the use of *Helicobacter pylori* therapy containing clarithromycin and acute neuropsychiatric events?

Findings In this study of 66 559 patients, 1824 patients receiving *H pylori* treatment with clarithromycin had an incident neuropsychiatric event, a 4-fold statistically significant increase during a 14-day treatment period. The risk was not raised before treatment and returned to baseline incidence after treatment.
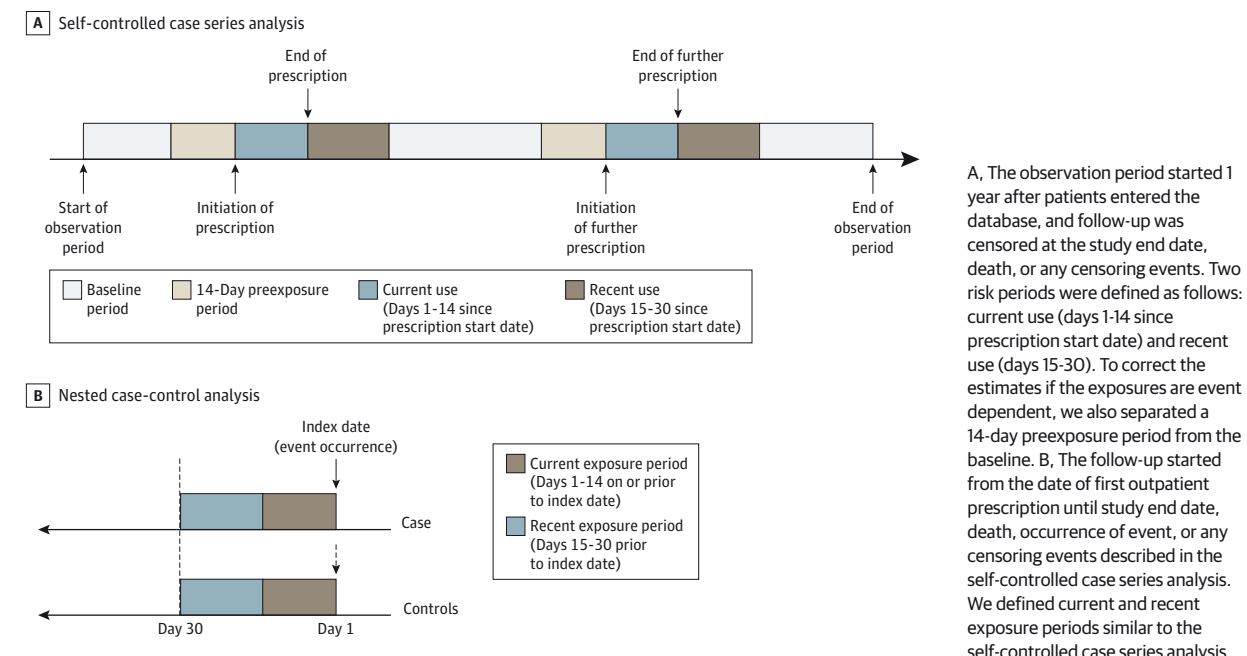
Meaning The risk of neuropsychiatric events during the use of *H pylori* treatment with clarithromycin is short-term and will usually resolve after cessation of treatment and psychiatric intervention can be avoided.

pital Authority, the Clinical Management System was established as a clinical workstation to provide access to wards and ambulatory settings, as well as laboratory, radiology, and pharmacy systems in public hospitals and clinics. The clinical information is directly recorded into the Clinical Management System by clinicians and other health care professionals. The health records in the Clinical Management System are then routinely transferred to the Clinical Data Analysis and Reporting System for audit and research purposes. Since 1993, the electronic health records in the Clinical Data Analysis and Reporting System have included patient demographics and clinical data such as diagnosis, operation, prescription use, accident and emergency visits, and outpatient and inpatient visits. A unique patient identifier is generated for each individual patient to link all medical records. To protect patient confidentiality, all medical records are anonymized. This database has been used to conduct high-quality epidemiological studies in Hong Kong[26,29,30] and multinational pharmacovigilance studies.[31,32]

Study Design

The self-controlled case series method is a case-only approach for eliminating between-person confounding. It compares the rate of outcomes in risk periods with baseline within individuals, derived from cohort methodology.[33] The analysis is based on individuals who must have had both the exposure and the event. In Hong Kong, *H pylori* infection is diagnosed during endoscopy by rapid urease test or histologic analysis before treatment, and empirical therapy is not a common practice. In this study, the exposure of interest was *H pylori* therapy containing clarithromycin in the outpatient setting. We defined it as coprescription of clarithromycin with either amoxicillin or metronidazole and one of the PPIs with British National Formulary recommended doses (eTable 1 in the Supplement) because there are no other indications for this coprescription. The coprescriptions must share the same prescription start date with an overlapping duration of 7 to 14 days. We estimated the treatment duration by adding 1 day to the difference of prescription end date and prescription start date. The application of a strict definition increases the precision of identifying such exposure to avoid introducing bias from identifying other acute infection indications.

Figure. Study Analyses

A Self-controlled case series analysis

A, The observation period started 1 year after patients entered the database, and follow-up was censored at the study end date, death, or any censoring events. Two risk periods were defined as follows: current use (days 1-14 since prescription start date) and recent use (days 15-30). To correct the estimates if the exposures are event dependent, we also separated a 14-day preexposure period from the baseline. B, The follow-up started from the date of first outpatient prescription until study end date, death, occurrence of event, or any censoring events described in the self-controlled case series analysis. We defined current and recent exposure periods similar to the self-controlled case series analysis.

The primary outcome was the first recorded acute composite neuropsychiatric events, while secondary outcomes were the first recorded psychotic events and first recorded cognitive impairment as principal diagnosis for an inpatient or accident and emergency admission. All cases were identified according to the *International Classification of Diseases, Ninth Revision (ICD-9)* (eTable 2 in the Supplement). Based on the symptoms (ie, psychosis, delirium, mood, and sleep disturbances) described in the identified case reports,[19-25] a list of diagnostic codes that describes acute and possibly drug-induced clinical conditions for neuropsychiatric events was developed and independently reviewed by 2 local clinical psychiatrists (E.H.M.L. and W.C.C.). To enhance the reliability and validity of the case definition, a final list of diagnostic codes was then confirmed by consensus in meetings involving psychiatrists and researchers.

Patients who were at least 18 years old and had received at least 1 outpatient prescription of *H pylori* therapy containing clarithromycin during the study period (from January 1, 2003, to December 31, 2012) were identified. If there was a preceding gap of more than 7 days with no prescription, this was defined as a new prescription. To remove those patients with more severe health issues identified on the prescription date, patients who received any clarithromycin prescription or inpatient therapy prior to the first outpatient therapy were excluded. Follow-up was censored if patients received a clarithromycin prescription or inpatient therapy after the first outpatient therapy. This cohort of patients with *H pylori* therapy containing clarithromycin was also described in our previous publication.[26]

The observation period (**Figure**) started 1 year after patients entered the database, and follow-up was censored at the study end date, death, or any censoring events described

herein. Because treatment duration for each prescription ranged from 7 to 14 days, 2 risk periods were defined as follows: current use (days 1-14 since prescription start date) and recent use (days 15-30). To correct the estimates if the exposures are event dependent, we also separated a 14-day preexposure period from the baseline. This could address bias resulting from change in baseline incidence in the period just before the exposure if the event alters the likelihood of subsequent exposure.

Statistical Analyses and Sensitivity Analyses
Incidence rate ratios (IRRs) with age adjustment in single years were estimated using the conditional Poisson regression, comparing the rate of events during risk periods with that during baseline.

Because events identified on the first day of prescription might reflect the underlying health status of the patient rather than being induced by the therapy of interest, we conducted a sensitivity analysis by either removing the first day of prescription from current use of treatment or including it in the preexposure period (ie, we considered only days 2-14). We carried out additional sensitivity analysis to divide current use into 2 periods (days 1-7 and days 8-14). Another sensitivity analysis was conducted to include other *ICD-9* codes, which have nonspecific descriptions for psychotic events to test the robustness of the outcome identification (eTable 2 in the Supplement). Because metronidazole has infrequently been reported to be associated with neuropsychiatric events,[34-37] we conducted additional sensitivity analyses that included patients with *H pylori* therapy containing clarithromycin, amoxicillin, and PPIs only.

We estimated the crude absolute risk with 95% CIs for all outcomes as the number of events occurred during current use

divided by the total number of identified outpatient *H pylori* therapy containing clarithromycin.[30]

A post hoc nested case-control analysis among patients with outpatient *H pylori* therapy containing clarithromycin was conducted to validate the findings of the primary outcome in the self-controlled case series analysis. Patients were eligible if they were at least 18 years old at the prescription start date. Follow-up commenced from the date of first outpatient prescription until study end date, death, occurrence of event, or any censoring events described in the self-controlled case series analysis. We identified cases within the study period and then randomly matched 4 controls at most to each case by year of birth and sex using the incidence density sampling method. We defined current and recent exposure periods similar to the self-controlled case series analysis (Figure). Only the current exposure period was considered if the prescription spanned the current and recent exposure periods. Using conditional logistic regression, we estimated the crude and adjusted odds ratios with adjusted variables of psychiatric service use in public sector and the use of other drugs (diuretics, calcium channel blockers, bronchodilators, psychotropic drugs, antiepileptic drugs, antiparkinsonian drugs, antiretroviral drugs, oral corticosteroids, and nonsteroidal anti-inflammatory drugs) in the previous 365 days prior to the event.

The statistical analyses were conducted independently by 2 investigators (A.Y.S.W. and C.S.L.C.) for quality assurance. All statistical analyses were performed with the use of SAS software (version 9.3; SAS Institute Inc) and R (version 3.2.0; http://www.R-project.org).

Results

A total of 66 559 patients who were at least 18 years old and had received at least 1 outpatient prescription of *H pylori* therapy containing clarithromycin during the study period were identified. Their mean (SD) age at cohort entry was 50.8 (14.8 years); their mean age at first exposure was 55.4 (14.8) years, and 30 910 were male (46.4%). A total of 1824 patients were identified with a first recorded composite neuropsychiatric event (eFigure 1 in the Supplement), 354 with a first recorded psychotic event, and 726 with a first recorded cognitive impairment within the study period (**Table 1**). eTable 3 in the Supplement shows the top 3 most frequently reported diagnostic codes for each outcome.

Table 2 shows the IRRs of all outcomes. Comparing current use with the baseline, the IRR for composite neuropsychiatric events was 4.12 (95% CI, 2.94-5.76) (35 events during 72 person-years) and was reduced to 0.95 (95% CI, 0.49-1.83) during recent use (9 events during 82 person-years). No increased risk could be found during the preexposure period (14 events during 72 person-years) vs baseline (1766 events during 16 665 person-years). For psychotic events, an increased IRR of 5.42 (95% CI, 2.77-10.60) was found during current use (9 events during 14 person-years) but not in other risk periods vs baseline. The risk of cognitive impairment was nearly 2- to 3-fold higher during current use (9 events during 28 person-years; IRR, 2.63 [95% CI, 1.36-5.09]), but there was no evidence of increased risk for all other risk periods. Similar to the primary analyses, increased IRRs were also found during days 2 to 14 since the prescription start date for all outcomes vs base-

Table 1. Demographic Information of the Final Cohort of the Included Patients

Characteristic	Composite Neuropsychiatric Events	Psychotic Events	Cognitive Impairment
Patients receiving therapy, No.	1824	354	726
Age, mean (SD), y			
At cohort entry	54.4 (15.8)	55.4 (17.3)	61.6 (14.6)
At exposure	59.1 (15.6)	59.8 (16.8)	66.2 (14.2)
At time of event	59.8 (16.2)	60.9 (17.7)	67.6 (14.8)
Male sex, No. (%)	833 (45.7)	170 (48.0)	394 (54.3)

Table 2. Results of Self-controlled Case Series Analysis for the Use of *Helicobacter pylori* Therapy Containing Clarithromycin and Risk of Neuropsychiatric Events

Type of Event	Person-years	Events, No.	Age-Adjusted IRR (95% CI)
Composite neuropsychiatric events (n = 1824)			
Baseline	16 665	1766	NA
14 Days before prescription	72	14	1.63 (0.96-2.77)
Days 1-14 since prescription start date	72	35	4.12 (2.94-5.76)
Days 15-30 since prescription start date	82	9	0.95 (0.49-1.83)
Psychotic events (n = 354)			
Baseline	3117	340	NA
14 Days before prescription	14	3	1.78 (0.57-5.56)
Days 1-14 since prescription start date	14	9	5.42 (2.77-10.60)
Days 15-30 since prescription start date	16	2	1.09 (0.27-4.40)
Cognitive impairment (n = 726)			
Baseline	6583	705	NA
14 Days before prescription	29	6	1.71 (0.76-3.82)
Days 1-14 since prescription start date	28	9	2.63 (1.36-5.09)
Days 15-30 since prescription start date	32	6	1.56 (0.70-3.50)

Abbreviations: IRR, incidence rate ratio; NA, not applicable.

line (eTables 4 and 5 in the Supplement). The sensitivity analysis in which current use was divided into days 1 to 7 and days 8 to 14 still showed an increased risk for primary outcome and psychotic events. For cognitive impairment, an increased risk was observed from days 1 to 14 but not for days 1 to 7. The insignificant finding for the former period was likely due to unstable estimates resulting from small sample size (eTable 6 in the Supplement). After including the nonspecific ICD-9 codes in the sensitivity analysis, a similar temporal pattern could also be observed (eTable 7 in the Supplement). For additional analyses that considered only therapy containing clarithromycin, amoxicillin, and PPIs, increased risk during current use was still observed for all outcomes (eTable 8 in the Supplement).

A total of 77 758 outpatient *H pylori* therapy containing clarithromycin prescriptions were identified during the study period. The crude absolute risk of neuropsychiatric events, psychotic events, and cognitive impairment during current use of therapy were 0.45 (95% CI, 0.32-0.63), 0.12 (95% CI, 0.06-0.22), and 0.12 (95% CI, 0.06-0.22) per 1000 prescriptions, respectively.

Similar to self-controlled case series analysis, we found increased crude and adjusted odds ratios during treatment in the nested case-control analysis (eTables 9 and 10 in the Supplement).

Discussion

Relative to baseline incidence, the incidence of neuropsychiatric events was approximately 4-fold higher during the current use of *H pylori* therapy containing clarithromycin. Notably, the risk returned to baseline incidence during recent use of treatment, suggesting that the risk of neuropsychiatric events is short-term. In our previous study,[26] we highlighted the cardiovascular safety issues of clarithromycin and recommended that clarithromycin should be prescribed with caution in patients with high baseline cardiovascular risk. In this study, however, given the low absolute neuropsychiatric risk, an abrupt change in prescribing practice based on the observed increase in neuropsychiatric events is not suggested, particularly in the absence of better treatment alternatives. Similar to our previous study,[26] clinicians should also be well informed of transient neuropsychiatric events associated with this treatment. Such transient neuropsychiatric events will usually resolve spontaneously after treatment cessation, and psychiatric interventions can be avoided.

Because the self-controlled case series analysis is suitable for investigating the association between transient exposure and acute outcome,[33] this method was used in our study to eliminate time-invariant confounders. However, similar to other observational study designs, it is still susceptible to time-varying confounders, such as a short-term change in health status and the use of other drugs. To address this, we further adjusted for the use of other drugs in the nested case-control study analysis and found similar results.

Notably, acute infection (eg, pneumonia) might lead to substantial short-term increased risk of neuropsychiatric events.[38] Because *H pylori* is by nature a chronic infection, it is unlikely

to temporally change the incidence of neuropsychiatric events shortly before and after treatment initiation. Therefore, it is less likely to lead to a spurious short-term association between therapy and outcome. Another consideration was that if the neuropsychiatric events were due to the infection rather than therapy, we would have observed an increased risk during the preexposure period. Because this was not observed during the preexposure period in any of the analyses, we can conclude that the short-term increased risk of neuropsychiatric events is more likely to be attributable to the therapy than the infection itself.

Because we investigated *H pylori* therapy as the exposure, we could not pinpoint which drug in the regimen contributed to the neuropsychiatric events in our study. We hypothesized that clarithromycin is the most probable drug because very limited evidence suggested that neuropsychiatric events are associated with amoxicillin[39,40] or PPIs.[41-43] We also conducted sensitivity analyses to test the robustness of the result when metronidazole (for which there are some reports of association with neuropsychiatric events compared with other ingredients)[34-37] was removed from the analysis. The increased risk of neuropsychiatric events during current use still remained. In addition, a case report raised an interesting and important case in which a patient who should have received clarithromycin, lansoprazole, and amoxicillin for *H pylori* eradication inadvertently took ciprofloxacin instead of clarithromycin for a week owing to a dispensing error. The neuropsychiatric symptoms did not appear until 2 days after the patient changed back to the correct regimen (ie, clarithromycin).[25] Moreover, all the identified cases remitted 1 to 3 days after treatment discontinuation in the current literature.[19-25] Therefore, clarithromycin is the most probable culprit to increase neuropsychiatric risk. Although the potential effect of other drugs in the regimen could not be entirely ruled out, the evidence in our study still suggests that *H pylori* therapy containing clarithromycin as a whole increases short-term neuropsychiatric risk. This should be brought to the attention of prescribers. Further research is needed to evaluate the neuropsychiatric risk associated with different drugs in the regimen.

While macrolides diffusion to the central nervous system is considered to be poor,[44] the mechanism pathway governing its neuropsychiatric adverse effect is still unknown. Several explanations have been postulated, including direct toxic effects on the central nervous system by the active metabolite of clarithromycin (14-hydroxyclarithromycin), alterations in the metabolism of cortisol, prostaglandin, and other hormones associated with neuropsychiatric events, as well as interactions with neurotransmitters (glutamate and gamma-aminobutyric acid).[17,18] Further research is warranted to explore these hypotheses.

With reference to the temporal association and dosage, our findings are consistent with the results of many potential cases of clarithromycin-induced neuropsychiatric events, which were summarized in a review.[17] This review reported that neuropsychiatric symptoms manifested 1 to 10 days after receiving clarithromycin treatment, which is in line with our results. It also seems that high-dose clarithromycin (>1000 mg/d for treatment of *Mycobacterium avium* complex or

Mycobacterium abscessus lung infection) is not a necessary condition for neuropsychiatric events.[3,17,18,45] In our study, patients were prescribed the British National Formulary usual recommended dose (1000 mg/d or 500 mg/d).

To our knowledge, this is the first population-based study investigating this association using the self-controlled case series method to eliminate any fixed residual confounding. In addition, comprehensive linkages between public hospitals and outpatient clinics health services provided accurate case ascertainment in our database. Although the retrospective nature of our study precludes us from conducting prospective structured interviews to confirm diagnoses, inaccuracies in the ascertainment of cases are minimized because the diagnostic codes for each inpatient case in public hospitals in Hong Kong are verified and input in a standardized format in the computerized clinical management system by the treating clinician. We used discharge diagnoses for case identification to ensure that a thorough diagnostic review had been performed by the clinical team involving senior specialists and the treating clinician. Previous studies using similar methods to ascertain other clinical outcomes by the Clinical Data Analysis and Reporting System have reported high positive predictive values for events such as gastrointestinal tract bleeding,[29] myocardial infarction,[26] stroke,[26] autism spectrum disorders, and attention-deficit/hyperactivity disorder (K. K. Man; email communication; February 17, 2016). Moreover, if we assume the likelihood of diagnostic inaccuracy was the same during the risk period and baseline, this error would underestimate the association and increase the likelihood of a negative finding. Our study is limited to patients with *H pylori* infection; therefore, our findings are less generalizable to patients who have been prescribed clarithromycin for other indications. Another limitation is that we were not able to determine drug adherence owing to limited data availability, and this might lead to some degree of bias from misclassification of exposure. In addition, clinical data from private health care setting are not available in our database. However, we included patients who used public health care services at least twice. These included patients were very likely to use public health care services instead of private services, because the public health care cost is heavily subsidized by the government.

Conclusions

This study found a short-term increased risk of neuropsychiatric events associated with current use of *H pylori* therapy containing clarithromycin, and the temporal increased risk is in full concordance with the treatment duration. Such transient neuropsychiatric events will usually resolve spontaneously after treatment cessation and psychiatric interventions can be avoided.

REFERENCE

1. Ho P, Wong S. Reducing bacterial resistance with IMPACT. 4th ed. 2012. http://www.chp.gov.hk/files/pdf/reducing_bacterial_resistance_with_impact.pdf. Accessed September 7, 2015.

2. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection: the Maastricht IV/Florence Consensus Report. *Gut.* 2012;61(5):646-664.

3. Nightingale SD, Koster FT, Mertz GJ, Loss SD. Clarithromycin-induced mania in two patients with AIDS. *Clin Infect Dis.* 1995;20(6):1563-1564.

4. Pollak PT, Sketris IS, MacKenzie SL, Hewlett TJ. Delirium probably induced by clarithromycin in a patient receiving fluoxetine. *Ann Pharmacother.* 1995;29(5):486-488.

5. Steinman MA, Steinman TI. Clarithromycin-associated visual hallucinations in a patient with chronic renal failure on continuous ambulatory peritoneal dialysis. *Am J Kidney Dis.* 1996;27(1):143-146.

6. Cone LA, Sneider RA, Nazemi R, Dietrich EJ. Mania due to clarithromycin therapy in a patient who was not infected with human immunodeficiency virus. *Clin Infect Dis.* 1996;22(3):595-596.

7. Finkenbine R, Gill HS. Case of mania due to prednisone-clarithromycin interaction. *Can J Psychiatry.* 1997;42(7):778.

8. Abouesh A, Hobbs WR. Clarithromycin-induced mania. *Am J Psychiatry.* 1998;155(11):1626.

9. Mermelstein HT. Clarithromycin-induced delirium in a general hospital. *Psychosomatics.* 1998;39(6):540-542.

10. Geiderman JM. Central nervous system disturbances following clarithromycin ingestion. *Clin Infect Dis.* 1999;29(2):464-465.

11. Tse KC, Li FK, Tang S, Lam MF, Chan TM, Lai KN. Delusion of worm infestation associated with clarithromycin in a patient on peritoneal dialysis. *Perit Dial Int.* 2001;21(4):415-416.

12. Jiménez-Pulido S, Navarro-Ruiz A, Sendra P, Martínez-Ramírez M, Garcia-Motos C, Montesinos-Ros A. Hallucinations with therapeutic doses of clarithromycin. *Int J Clin Pharmacol Ther.* 2002;40(1):20-22.

13. Brooks JO III, Hoblyn JC. Secondary mania in older adults. *Am J Psychiatry.* 2005;162(11):2033-2038.

14. Vicente de Vera C, García M, Pifarre Teixido R, Barbe F. Delirium induced by clarithromycin in a patient with community-acquired pneumonia. *Eur Respir J.* 2006;28(3):671-672.

15. Kouvelou E, Pourzitaki C, Aroni F, Papazisis G, Kouvelas D. Acute psychosis induced by clarithromycin in a healthy adult? *J Clin Psychopharmacol.* 2008;28(5):579-580.

16. Liu EY, Vasudev A. Mania induced by clarithromycin in a geriatric patient taking low-dose prednisone. *Prim Care Companion CNS Disord.* 2014;16(3):PCC.14l01626.

17. Bandettini di Poggio M, Anfosso S, Audenino D, Primavera A. Clarithromycin-induced neurotoxicity in adults. *J Clin Neurosci.* 2011;18(3):313-318.

18. Aboueesh A, Stone C, Hobbs WR. Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol*. 2002;22(1):71-81.

19. Gómez-Gil E, García F, Pintor L, Martínez JA, Mensa J, de Pablo J. Clarithromycin-induced acute psychoses in peptic ulcer disease. *Eur J Clin Microbiol Infect Dis*. 1999;18(1):70-71.

20. Neff NE, Kuo G. Acute manic psychosis induced by triple therapy for H. pylori. *J Am Board Fam Pract*. 2002;15(1):66-68.

21. Ortíz-Domínguez A, Berlanga C, Gutiérrez-Mora D. A case of clarithromycin-induced manic episode (antibiomania). *Int J Neuropsychopharmacol*. 2004; 7(1):99-100.

22. Htut Y, Kunanayagam S, Poi PJ. Clarithromycin induced psychosis. *Med J Malaysia*. 2006;61(2):263.

23. Shah M, Subhani M, Rizvon K, Mustacchia P. Transient psychotic episode induced by *Helicobacter pylori* triple therapy treatment. *Case Rep Gastroenterol*. 2012;6(2):381-386.

24. Feng Z, Huang J, Xu Y, Zhang M, Hu S. Dissociative disorder induced by clarithromycin combined with rabeprazole in a patient with gastritis. *J Int Med Res*. 2013;41(1):239-243.

25. Dinca EB, Skinner A, Dinca RV, Tudose C. The dangers of gastritis: a case of clarithromycin-associated brief psychotic episode. *J Nerv Ment Dis*. 2015;203(2):149-151.

26. Wong AY, Root A, Douglas IJ, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ*. 2016; 352:h6926.

27. HAHO/ITD. *Clinical Data Analysis & Reporting System (CDARS) User's Manual*. 2nd ed. Hong Kong: Hospital Authority; 2003:3.

28. Hospital Authority. Hospital Authority: Introduction. 2015. http://www.ha.org.hk/visitor/ha _visitor_index.asp?Parent_ID=10004&Content_ID =10008&Ver=HTML. Accessed November 25, 2015.

29. Chan EW, Lau WC, Leung WK, et al. Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a population-based study. *Gastroenterology*. 2015;149(3):586-95.e3.

30. Chui C, Chan E, Wong A, Root A, Douglas IJ, Wong IC. Association between oral fluoroquinolones and seizures: a self-controlled case series study. *Neurology*. In press.

31. Pratt N, Chan EW, Choi NK, et al. Prescription sequence symmetry analysis: assessing risk, temporality, and consistency for adverse drug reactions across datasets in five countries. *Pharmacoepidemiol Drug Saf*. 2015;24(8):858-864.

32. Roughead EE, Chan EW, Choi NK, et al. Variation in association between thiazolidinediones and heart failure across ethnic groups: retrospective analysis of large healthcare claims databases in six countries. *Drug Saf*. 2015;38(9):823-831.

33. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med*. 2006; 25(10):1768-1797.

34. Kuriyama A, Jackson JL, Doi A, Kamiya T. Metronidazole-induced central nervous system toxicity: a systematic review. *Clin Neuropharmacol*. 2011;34(6):241-247.

35. Khandheria M, Snook E, Thomas C. Psychotic episode secondary to metronidazole use. *Gen Hosp Psychiatry*. 2014;36(2):231.e3-231.e4.

36. Voth AJ. Possible association between metronidazole and agitated depression. *Can Med Assoc J*. 1969;100(21):1012-1013.

37. Mahl TC, Ummadi S. Metronidazole and mental confusion. *J Clin Gastroenterol*. 2003;36(4):373-374.

38. Targum SD. Treating psychotic symptoms in elderly patients. *Prim Care Companion J Clin Psychiatry*. 2001;3(4):156-163.

39. Oliver DJ. Hallucinations associated with amoxicillin? a case report. *Practitioner*. 1984;228 (1396):884.

40. Stell IM, Ojo OA. Amoxicillin-induced hallucinations: a variant of Hoigne's syndrome? *Br J Clin Pract*. 1996;50(5):279.

41. Alfonzo CA, Bobo WV, Almond MD. Not a usual suspect: rabeprazole therapy presenting as a severe neuropsychiatric illness: case report. *Int J Psychiatry Med*. 2003;33(3):311-315.

42. Hanneken AM, Babai N, Thoreson WB. Oral proton pump inhibitors disrupt horizontal cell-cone feedback and enhance visual hallucinations in macular degeneration patients. *Invest Ophthalmol Vis Sci*. 2013;54(2):1485-1489.

43. Akter S, Hassan MR, Shahriar M, Akter N, Abbas MG, Bhuiyan MA. Cognitive impact after short-term exposure to different proton pump inhibitors: assessment using CANTAB software. *Alzheimers Res Ther*. 2015;7(1):79.

44. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev*. 2010;23(4):858-883.

45. Wallace RJ Jr, Brown BA, Griffith DE. Drug intolerance to high-dose clarithromycin among elderly patients. *Diagn Microbiol Infect Dis*. 1993;16 (3):215-221.