Title: Acute neuropsychiatric events associated with *Helicobacter pylori* therapy containing-clarithromycin: a population-based study

Angel YS Wong, BSc[1], Ian CK Wong, PhD[1, 2], Celine SL Chui, MSc[1], Edwin HM Lee, FHKCPsych[3], WC Chang, FHKCPsych[3], Eric YH Chen, MD[3], Wai K Leung, MD[4], Esther W Chan, PhD[1]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

[2]Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom

[3]Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

[4]Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

Authors' contributions: AW, IW, EC were responsible for the conception and design of the study. All authors contributed to the analysis and the drafting, revision, and final approval of the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest disclosures: All authors report no financial relationships with commercial interests and no competing interests.

Ethics approval: The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (IRB reference number: UW 14-032).

Correspondence to:

Dr. Esther W Chan

Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.
Telephone: +852 3917 9029
Email: ewchan@hku.hk

Professor Ian C K Wong

Research Department of Practice and Policy
UCL School of Pharmacy 29-39 Brunswick Square
London WC1N 1AX
Telephone: +44 207 753 5966
Email: i.wong@ucl.ac.uk

No of words in the text: 3000 (max: 3000) Date of revision: 15th March 2016

Abstract

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 out-patient setting. Study subjects aged ≥18 at cohort entry, must have both exposure to *H. pylori* therapy containing-clarithromycin and their first recorded neuropsychiatric events from January 1, 2003 to December 31, 2012. A *post-hoc* nested case-control analysis was also performed on 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 pre-exposure period, current use(day 1-14 since prescription start date) and recent use(day 15-30). Age adjusted incidence rate ratios(IRR) were estimated using the conditional Poisson regression.

Results: Of 66 559 patients who had at least one out-patient prescription of *H. pylori* therapy containing-clarithromycin, 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 pre-exposure period(14 events during 72 person years; IRR, 1.63; 95% CI, 0.96-2.77) versus baseline(1766

events during 16 665 person-years). Similarly, both the risk of psychotic events and cognitive impairment increased during current use versus baseline although this subsequently returned to baseline incidence levels during recent use. The crude absolute risk 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.

Conclusions and relevance: This study shows evidence of a short-term increased risk of neuropsychiatric events associated with *H. pylori* therapy containing-clarithromycin.

No of words in abstract: 345 (max: 350)

Introduction

Clarithromycin is used for the treatment of respiratory infections including community acquired pneumonia.[1] It is also commonly prescribed in combination with amoxicillin/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 two patients with acquired immune deficiency syndrome 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] The majority of the reported neuropsychiatric symptoms were related to psychotic manifestations and cognitive disturbances.[17] In these reports, the neuropsychiatric symptoms appeared 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 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, no population-based study to date 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. Due to different underlying neuropsychiatric risks, indication bias might result in findings of non-causal 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 explore the safety considerations of clarithromycin in this study, by investigating the association between *H. pylori* therapy containing-clarithromycin and acute neuropsychiatric events.

Method

Data sources

The data was 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 Out-patient Clinics, and 73 General Out-patient Clinics.[28] More than seven million local residents have access to these primary, secondary and tertiary public healthcare services through seven hospital clusters.[27] In the Hospital 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 healthcare 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 included patient demographics and clinical data such as diagnosis, operation, prescription use, accident &

emergency, out-patient and in-patient 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 histology 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 out-patient setting. We defined it as co-prescription of clarithromycin with either amoxicillin or metronidazole, and one of the PPIs with British National Formulary recommended doses (eTable 1) as there are no other indications for this co-prescription. The co-prescriptions must share the same prescription start date with an overlapping duration of 7-14 days. We estimated the treatment duration by adding one 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.

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 in-patient or accident & emergency admission. All cases

were identified according to the 9th International Classification of Diseases (eTable 2 in the supplement). Based on the symptoms (i.e. psychosis, delirium, mood and sleep disturbances) described in the identified case reports[19-25], a list of diagnostic codes which describe acute and possibly drug-induced clinical conditions for neuropsychiatric events was developed and independently reviewed by two local clinical psychiatrists (EL and WC). 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 aged ≥18 years and received at least one out-patient 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. In order to remove those patients with more severe health issues identified on the prescription date, patients who received any clarithromycin prescription or in-patient therapy prior to the first out-patient therapy were excluded. Follow-up was censored if patients received a clarithromycin prescription or in-patient therapy after the first out-patient therapy. This cohort of patients with *H. pylori* therapy containing-clarithromycin was also described in our previous publication.[26]

The observation period (Figure 1) started one year after patients entered the database and follow-up was censored at the study end date, death, or any censoring events described above. As treatment duration for each prescription ranged from 7-14 days, two risk periods were defined as follows: current use (day 1-14 since prescription start date) and recent use (day 15-30). In order to correct the estimates if the exposures are event-dependent, we also separated a 14-day pre-exposure 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.

As 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 pre-exposure period (i.e. only consider day 2-14). We carried out additional sensitivity analysis to divide current use into two periods (day 1-7 and day 8-14). Another sensitivity analysis was conducted to include other ICD-9 codes, which have non-specific descriptions for psychotic events to test the robustness of the outcome identification (eTable 2). As 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% confidence interval for all outcomes as the number of events occurred during current use divided by the total number of identified out-patient *H. pylori* therapy containing-clarithromycin.[30]

A *post-hoc* nested case-control analysis among patients with out-patient *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 aged ≥18 at the

prescription start date. Follow-up commenced from the date of first out-patient 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 four 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 1). 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 two investigators (AW and CC) for quality assurance. All statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute) and R version 3.2.0 (www.R-project.org).

Results

A total of 1824 patients were identified with a first recorded composite neuropsychiatric event (eFigure 1), 354 with a first recorded psychotic event and 726 with a first recorded cognitive impairment within the study period (Table 1). The eTable 3 shows the top three most frequently reported diagnostic codes for each outcome.

Table 2 shows the IRRs of all outcomes. Comparing current use with the baseline, the IRR (95% CI) for composite neuropsychiatric events was 4.12(2.94-5.76) (35 events during 72 person-

years) and was reduced to 0.95(0.49-1.83) during recent use (9 events during 82 person-years). No increased risk could be found during the pre-exposure period (14 events during 72 person-years) versus baseline (1766 events during 16 665 person-years). For psychotic events, an increased IRR of 5.42(2.77-10.60) was found during current use (9 events during 14 person-years) but not in other risk periods versus baseline. The risk of cognitive impairment was nearly two- to three- fold higher during current use [9 events during 28 person-years; IRR, 2.63(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 day 2-14 since the prescription start date for all outcomes versus baseline (eTable 4 and 5). The sensitivity analysis where current use was divided into day 1-7 and 8-14 still showed an increased risk for primary outcome and psychotic events. For cognitive impairment, an increased risk was observed from day 1 to 14 but not for day 1-7. The insignificant finding for the latter period was likely due to unstable estimates resulting from small sample size (eTable 6). After including the non-specific ICD-9 codes in the sensitivity analysis, a similar temporal pattern could also be observed (eTable 7). For additional analyses that only considered therapy containing clarithromycin, amoxicillin and PPIs, increased risk during current use was still observed for all outcomes (eTable 8).

A total of 77 758 out-patient *H. pylori* therapy containing-clarithromycin prescriptions were identified during the study period. The crude absolute risk (95% CI) of neuropsychiatric events, psychotic events and cognitive impairment during current use of therapy were 0.45(0.32-0.63), 0.12(0.06-0.22) and 0.12(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 (eTable 9 and 10).

Discussion

Relative to baseline incidence, the incidence of neuropsychiatric events was approximately four-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, we highlighted the cardiovascular safety issues of clarithromycin and recommended that clarithromycin should be prescribed with caution in patients with high baseline cardiovascular risk.[26] 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.

As 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 (such as pneumonia) might lead to substantial short-term increased risk of neuropsychiatric events.[38] As *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 pre-exposure period. As this was not observed during the pre-exposure 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.

Since 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 as 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 where a patient who should have received clarithromycin, lansoprazole, and amoxicillin for *H. pylori* eradication inadvertently took ciprofloxacin instead of clarithromycin for a week due to a dispensing error. The neuropsychiatric symptoms did not appear until 2 days after the patient changed back the correct regimen (i.e. clarithromycin).[25] Moreover, all the identified cases remitted 1-3 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.

Whilst 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 1-10 days after receiving clarithromycin treatment, which is in line with our results. It also appears that high dose clarithromycin (more than 1000mg per day for treatment of *Mycobacterium avium* complex or *Mvcobacterium 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 (1000mg or 500mg per day).

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 out-patient 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 as the diagnostic codes for each inpatient case in public hospitals in Hong Kong are verified and inputted 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 methodology to ascertain other clinical outcomes by the Clinical Data Analysis and Reporting System have reported high positive predictive values for events such as gastrointestinal bleeding[29], myocardial infarction[26], stroke[26], Autism Spectrum Disorders and Attention Deficit Hyperactivity Disorder (Man KK, personal communication, 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 due to limited data availability and this might lead to some degree of bias from misclassification of exposure. In addition, clinical data from private healthcare setting is not available in our database. However, we included patients who used public healthcare services at least twice. These included patients were very likely to utilize public healthcare services instead of private services, as the public healthcare cost is heavily subsidized by the government.

C**onclusion**

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.

Acknowledgement: The authors would like to thank the Hong Kong Hospital Authority for access to data, Ms. Jody KP Chu, MClin Pharm, BPharm (Hons) from the Department of Pharmacology and Pharmacy, University of Hong Kong for clinical advice. We would also like to thank Ms. Lisa YL Wong, BSc (Hons), RGN, RHV, MJ (Master of Journalism) from European Medical Writers Association and Ms. Shweta Anand, BDS (Bachelor of Dental Surgery) from the Department of Pharmacology and Pharmacy, University of Hong Kong for proofreading the manuscript. Written permission has been obtained from all persons named in the acknowledgment. AW, CC, EWC and IW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AW and CC conducted and are responsible for the data-analysis.

All authors report no financial relationships with commercial interests and no competing interests. No funding or sponsorship is available for conducting this study. No sponsor organization or sponsor played role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Reference

1. Ho P, Wong S. Fourth Edition: Reducing bacterial resistance with IMPACT. 2012; http://www.chp.gov.hk/files/pdf/reducing_bacterial_resistance_with_impact.pdf. Accessed 7 September 2015.
2. Wong BCY. Update on Management of Helicobacter Pylori infection. *Medical Bulletin.* 2010;15(12):8-10.
3. Nightingale SD, Koster FT, Mertz GJ, Loss SD. Clarithromycin-induced mania in two patients with AIDS. *Clin Infect Dis.* Jun 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.* May 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.* Jan 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.* Mar 1996;22(3):595-596.
7. Finkenbine R, Gill HS. Case of mania due to prednisone-clarithromycin interaction. *Can J Psychiatry.* Sep 1997;42(7):778.
8. Abouesh A, Hobbs WR. Clarithromycin-induced mania. *Am J Psychiatry.* Nov 1998;155(11):1626.
9. Mermelstein HT. Clarithromycin-induced delirium in a general hospital. *Psychosomatics.* Nov-Dec 1998;39(6):540-542.
10. Geiderman JM. Central nervous system disturbances following clarithromycin ingestion. *Clin Infect Dis.* Aug 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.* Jul-Aug 2001;21(4):415-416.
12. Jimenez P, Navarro-Ruiz A, Sendra P, Martinez-Ramirez M, Garcia-Motos C, Montesinos-Ros A. Hallucinations with therapeutic doses of clarithromycin. *Int J Clin Pharmacol Ther.* Jan 2002;40(1):20-22.
13. Brooks JO, 3rd., Hoblyn JC. Secondary mania in older adults. *Am J Psychiatry.* Nov 2005;162(11):2033-2038.
14. Vicente de Vera C, Garcia M, Pifarre Teixido R, Barbe F. Delirium induced by clarithromycin in a patient with community-acquired pneumonia. *Eur Respir J.* Sep 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.* Oct 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).
17. Bandettini di Poggio M, Anfosso S, Audenino D, Primavera A. Clarithromycin-induced neurotoxicity in adults. *J Clin Neurosci.* Mar 2011;18(3):313-318.
18. Abouesh A, Stone C, Hobbs WR. Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol.* Feb 2002;22(1):71-81.
19. Gomez-Gil E, Garcia F, Pintor L, Martinez JA, Mensa J, de Pablo J. Clarithromycin-induced acute psychoses in peptic ulcer disease. *Eur J Clin Microbiol Infect Dis.* Jan 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.* Jan-Feb 2002;15(1):66-68.

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

22. Htut Y, Kunanayagam S, Poi PJ. Clarithromycin induced psychosis. *Med J Malaysia.* Jun 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.* May 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.* Feb 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.* Feb 2015;203(2):149-151.

26. Wong A, Root A, Doulgas I, 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. In: Hospital Authority, ed. 2.0 ed. Hong Kong2003:3.

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 25 November 2015.

29. Chan EW, Lau WC, Leung WK, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. *Gastroenterology.* Sep 2015;149(3):586-595 e583.

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.* 2016;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.* Aug 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.* Sep 2015;38(9):823-831.

33. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Statistics in medicine.* May 30 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.* Nov-Dec 2011;34(6):241-247.

35. Khandheria M, Snook E, Thomas C. Psychotic episode secondary to metronidazole use. *Gen Hosp Psychiatry.* Mar-Apr 2014;36(2):231 e233-234.

36. Voth AJ. Possible association between metronidazole and agitated depression. *Can Med Assoc J.* Jun 7 1969;100(21):1012-1013.

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

38. Targum SD. Treating Psychotic Symptoms in Elderly Patients. *Prim Care Companion J Clin Psychiatry.* Aug 2001;3(4):156-163.

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

40. Stell IM, Ojo OA. Amoxycillin-induced hallucinations--a variant of Hoigne's syndrome? *Br J Clin Pract.* Jul-Aug 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.* Feb 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, Sorgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clinical microbiology reviews.* Oct 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.* Mar-Apr 1993;16(3):215-221.

Table 1. Demographic information of the identified cohort of patients with *Helicobacter pylori* therapy containing-clarithromycin and final cohort of the included patients.

Patients with Helicobacter pylori therapy containing-clarithromycin						
N	66 559					
	Mean (years)			SD		
Age at cohort entry	50.8			14.8		
Age at first exposure	55.4			14.8		
	N (%)					
Male sex	30 910 (46.4)					
	Composite neuropsychiatric events		***Psychotic events***		***Cognitive impairment***	
N	1824		354		726	
	Mean (years)	SD	Mean (years)	SD	Mean (years)	SD
Age at cohort entry	54.4	15.8	55.4	17.3	61.6	14.6
Age at exposure	59.1	15.6	59.8	16.8	66.2	14.2
Age at time of event	59.8	16.2	60.9	17.7	67.6	14.8
	N (%)		N (%)		N (%)	
Male sex	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

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

Figure 1. Pictorial illustration for self-controlled case series analysis (panel a) and nested case-control analysis (panel b)