Clinical Infectious Diseases

MAJOR ARTICLE

Metronidazole-associated Neurologic Events: A Nested Case-control Study

Nick Daneman,[1,2,3,4] Yi Cheng,[1] Tara Gomes,[1,5] Jun Guan,[1] Muhammad M. Mamdani,[1,5] Farah E. Saxena,[1] and David N. Juurlink[1,2,3,6]

[1]ICES, Toronto, Ontario, Canada, [2]Sunnybrook Research Institute, Toronto, Ontario, Canada, [3]Division of Infectious Diseases, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, [4]Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada, [5]Li Ka Shing Knowledge Institute, St Michael's, University of Toronto, Toronto, Ontario, Canada, and [6]Division of Clinical Pharmacology and General Internal Medicine, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

(See the Editorial Commentary by Joseph Guglielmo on pages 2101-2.)

Background. Case reports have described instances of peripheral and central nervous system toxicity during treatment with metronidazole; however, no large-scale studies have examined this association.

Methods. We conducted a population-based nested case-control study of adults aged 66 years or older living in Ontario, Canada, between 1 April 2003 and 31 March 2017. Cases were individuals who attended hospital for any of cerebellar dysfunction, encephalopathy, or peripheral neuropathy within 100 days of a prescription for either metronidazole or clindamycin. We matched each case patient with up to 10 event-free control subjects who also received metronidazole or clindamycin. We used conditional logistic regression to test the association between metronidazole exposure and neurologic events, with clindamycin as the reference exposure.

Results. We identified 1212 cases with recent use of either metronidazole or clindamycin and 12 098 controls. Neurologic adverse events were associated with an increased odds of metronidazole exposure compared to clindamycin (odds ratio [OR], 1.72 [95% confidence interval {CI}, 1.53–1.94]), which persisted after accounting for patient demographics, comorbidities, and other medication exposures (adjusted odds ratio [aOR], 1.43 [95% CI, 1.26–1.63]). We found a consistent association limited to either central (aOR, 1.46 [95% CI, 1.27–1.68]) or peripheral (aOR, 1.34 [95% CI, 1.02–1.76]) nervous system events. Among metronidazole recipients, the overall incidence of neurologic events at 100 days was approximately 0.25%.

Conclusions. Metronidazole is associated with an increased risk of adverse peripheral and central nervous system events relative to clindamycin. Clinicians and patients should be aware of these rare but potentially serious adverse events.

Keywords. metronidazole; encephalopathy; cerebellar syndrome; peripheral neuropathy; pharmacoepidemiology.

Metronidazole, a nitroimidazole antimicrobial, was initially indicated for the management of parasitic infections, such as *Trichomonas*, *Entamoeba*, and *Giardia* species, but was subsequently determined to have activity against a range of anaerobic bacteria [1]. It is now one of the most commonly used antimicrobial agents [2, 3], and is a key treatment for anaerobic components of abscesses at all body sites, as well as targeted treatment of specific pathogens such as *Helicobacter pylori* and *Clostridioides difficile*.

Metronidazole-induced encephalopathy was first reported in 1977. In that case, a 19-year-old woman developed disorientation and short-term memory loss after 7 days of treatment for *Trichomonas* infection [4]. Nearly 100 case reports of suspected metronidazole neurotoxicity have subsequently been published, including both peripheral and central nervous system (CNS) abnormalities [5–10]. The former are typically characterized by slowly progressive, symmetric distal sensory neuropathy with predominantly small fiber involvement, often with severe pain, and often leading to permanent disability [8]. CNS involvement includes nonspecific encephalopathies, or, more commonly, a distinctive syndrome of cerebellar dysfunction characterized by dysarthria, ataxia, dysmetria, and nystagmus [6]. All such cases have been accompanied by imaging abnormalities, with cerebellar dentate nuclei lesions being the most characteristic finding [11]. Unlike peripheral neuropathy, CNS complications are usually reversible, with most patients experiencing at least some improvement and two-thirds experiencing complete resolution [8, 12].

Despite these reports of metronidazole-associated neurotoxicity, no population-based studies have formally examined this association. We explored this phenomenon, examining the association between metronidazole use and nervous system toxicity relative to clindamycin.

METHODS

General Study Design

We conducted a population-based nested case-control study involving older adults living in Ontario between 1 April 2003

Received 29 October 2019; editorial decision 5 March 2020; accepted 6 April 2020; published online April 18, 2020.

Correspondence: N. Daneman, Division of Infectious Diseases, Sunnybrook Health Sciences Centre, University of Toronto, ICES, Public Health Ontario, 2075 Bayview Ave, G-wing Room 106, Toronto, ON M4N 3M5, Canada (nick.daneman@sunnybrook.ca).

Clinical Infectious Diseases® 2021;72(12):2095–100

DOI: 10.1093/cid/ciaa395

and 31 March 2017. We defined cases as patients with incident central or peripheral nervous system disease, and with receipt of metronidazole or clindamycin, but not both, in the preceding 100 days. We matched each case with up to 10 event-free controls who had also received metronidazole or clindamycin in the preceding 100 days. We chose clindamycin as the comparator because, like metronidazole, it is a widely used oral agent for the treatment of anaerobic infections.

Data Sources

We used health administrative databases linked using unique encoded identifiers and analyzed at ICES, an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement. In Ontario, Canada's most populous province, these well-validated databases have been used extensively for antibiotic research [13, 14], and have been particularly useful for identifying and characterizing rare antibiotic-related adverse events [15, 16]. The Ontario Drug Benefit database identifies all outpatient prescription medications dispensed to Ontarians over the age of 65, and has an accuracy exceeding 99% in comparison to the reference standard of pharmacy chart review [17]. The Canadian Institute for Health Information (CIHI) Discharge Abstract Database captures information for all hospitalizations, the CIHI Same Day Surgery database captures patient visits to hospital and community-based ambulatory care (day surgery, outpatient clinics, and emergency departments), the CIHI National Ambulatory Care Reporting System Database captures information for all emergency department visits, and the Ontario Health Insurance Plan database records all physician services. These health administrative databases were used to identify specific comorbidities experienced prior to the index date (defined below), such as liver disease (past 2 years), alcohol use disorder (past 3 years), and any renal dysfunction (past year); the Ontario Diabetes Database was used to identify those who ever had diabetes mellitus. The Registered Person Database provided vital statistics and demographic information.

Definitions of Cases and Controls

Our study population included adults aged 66 years or older living in Ontario at any time in the 14-year period between 1 April 2003 and 31 March 2017. We defined cases as subjects with an emergency department visit or hospital admission for a new diagnosis of encephalopathy, cerebellar syndrome, or peripheral neuropathy, defined by *International Classification of Diseases, Tenth Revision* (*ICD-10*; Supplementary Table 1) as well as a prescription for metronidazole or clindamycin in the preceding 100 days. For each case, we identified up to 10 event-free control patients alive on the index date (the date of diagnosis of the case patient), matching on age (within 1 year), sex, and presence of a hospital encounter in the preceding 100 days.

Because our databases do not reliably identify inpatient drug exposures, we excluded case and control subjects with > 3 days in hospital in the 100 days preceding the index date. To focus on incident diagnoses, we also excluded subjects with any diagnosis of encephalopathy, cerebellar syndrome, or peripheral neuropathy in the preceding year.

Assessment of Antibiotic Exposure

The metronidazole and clindamycin exposures were defined as receipt of at least 1 prescription for the respective medication overlapping the 100 days prior to the index date. For secondary analyses examining cumulative metronidazole doses, we calculated the total mass of metronidazole (in grams) dispensed in the 100-day exposure period. The cumulative metronidazole doses were categorized after inspection of the overall distribution, as low (< 9.9 g), medium (9.9–19.9 g), or high (> 19.9 g).

Other Patient Characteristics

We identified demographic characteristics from the various databases, including age, sex, neighborhood income quintile, and rural vs urban residence. We expressed overall comorbidity based on the Deyo-Charlson comorbidity score [18, 19], and identified specific comorbidities that we anticipated might be associated with both metronidazole use and neurologic outcomes, including liver disease, alcohol use disorder, diabetes mellitus, and renal disease. We examined concomitant medications including antidepressant, antipsychotic, benzodiazepine, and opioid use in the year preceding the index date. Finally, we measured the patient's healthcare utilization history by determining the number of emergency department visits and hospitalizations in the preceding year.

Statistical Analysis

We compared patient characteristics between cases and controls, using χ^2 tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. We used conditional logistic regression to examine the association between neurologic toxicity and metronidazole exposure, with clindamycin as the reference exposure. We calculated an unadjusted odds ratio (OR), followed by an adjusted odds ratio (aOR) and 95% confidence interval (CI) using multivariable conditional logistic regression analysis with prespecified inclusion of all of the patient demographics, comorbidities, and concomitant medications.

In preplanned secondary analyses, we examined for dose-response by stratifying cumulative metronidazole dose into low, medium, and high categories using the definition above. We also conducted separate regression analyses for the central and peripheral nervous system outcomes.

Finally, to estimate the short-term incidence of neurologic toxicity following metronidazole use, we developed an inception cohort of first-time users of metronidazole, and identified the number of central and/or peripheral nervous system events within 100 days. All analyses were conducted according to strict privacy and confidentiality safeguards at ICES, using SAS software version 9.4 (Cary, North Carolina).

Ethical Considerations

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board. No patients or member of the general public were directly involved in the design, recruitment, or conduct of the study.

RESULTS

During the 14-year study period, we identified 78 439 older Ontarians with hospital visits for a first instance of encephalopathy, cerebellar dysfunction, or peripheral neuropathy. Among these, 1212 had exposure to either metronidazole or clindamycin, but not both, in the preceding 100 days (Figure 1). These subjects were successfully matched to 12 098 controls.

The baseline characteristics of cases and controls are displayed in Table 1. The median age was 78 years (interquartile range, 73–84 years) and 57% were women. The cases with neurologic events generally resided in lower-income neighborhoods, had higher healthcare utilization rates, and had higher rates of liver disease, alcohol use, diabetes mellitus, renal dysfunction, and concomitant pharmacotherapy with antidepressants, opioids, benzodiazepines, and antipsychotics.

In the crude analysis, neurologic adverse events were associated with an increased odds of metronidazole exposure compared to clindamycin (OR, 1.72 [95% CI, 1.53–1.94]) (Table 2). This association remained after accounting for demographics, healthcare utilization indices, comorbidities, and other medication exposures (aOR, 1.43 [95% CI, 1.26–1.63]; Table 2).

The association between metronidazole and neurologic events persisted in sensitivity analyses limited to CNS outcomes (encephalopathy and cerebellar dysfunction: aOR, 1.46 [95% CI, 1.27–1.68]) or peripheral neuropathy (aOR, 1.34 [95% CI, 1.02–1.76]; Table 2). In a post hoc sensitivity analysis limited to only cases of cerebellar dysfunction, the odds of metronidazole vs clindamycin use was consistent with the main study finding (aOR, 1.51 [95% CI, 1.31–1.75]).

We did not discern a clear dose-response effect. As compared to clindamycin use, receipt of low cumulative doses of metronidazole was associated with an increased risk of neurologic toxicity (aOR, 1.62 [95% CI, 1.37–1.92]), as was receipt of medium cumulative doses (aOR, 1.22 [95% CI, 1.03–1.45]) or high cumulative doses (aOR, 1.56 [95% CI, 1.24–1.95]) (Table 3). We reexamined for a cumulative dose response in separate analyses for CNS and peripheral nervous system toxicities, detecting none in either analysis (data not shown).

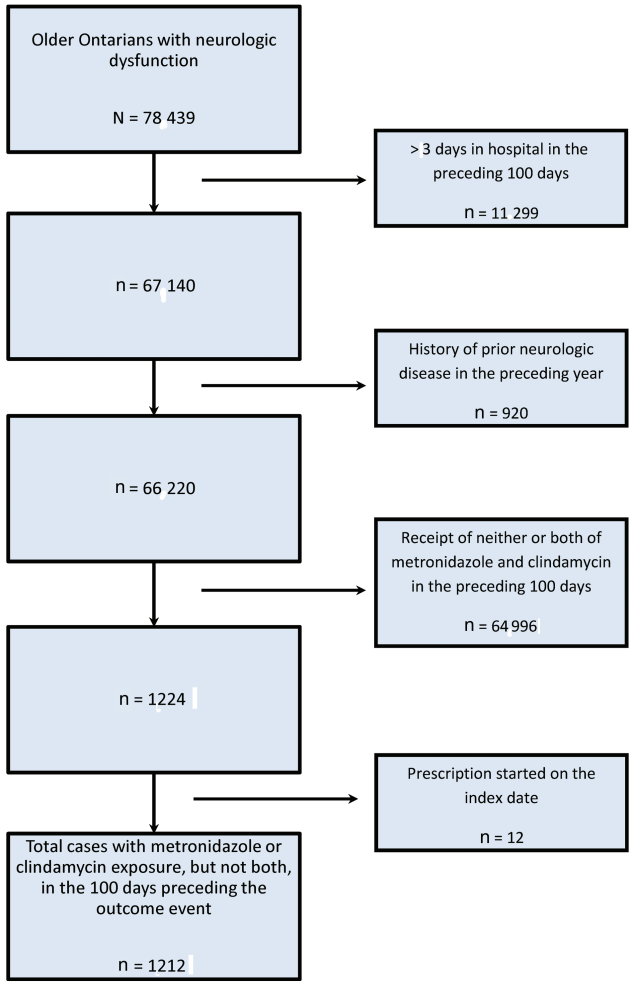

Figure 1. Study flowchart for identifying case patients.

Incidence of Neurologic Events Among Metronidazole Users

In an incident cohort of 336 425 older Ontarians receiving a first dose of metronidazole, 825 (0.25%) were diagnosed with a neurologic outcome event in the ensuing 100 days. CNS complications (encephalopathy or cerebellar dysfunction) were diagnosed in 665 (0.2%) patients, and peripheral neuropathy in 160 (0.05%) patients.

DISCUSSION

In this population-based nested case control study spanning 14 years, we found an association between adverse neurologic events and use of metronidazole as compared to clindamycin. The magnitude of this association was larger than that seen with other patient characteristics or other centrally active medications, and was consistent regardless of cumulative metronidazole dose. The incidence of these severe neurologic events

Table 1. Baseline Characteristics of Cases and Controls

Characteristics	Controls (n = 12 098)	Cases (n = 1212)	*P* Value
Age, y, mean ± SD	78.52 ± 7.41	78.59 ± 7.46	.73
Sex			
Female	6889 (56.9)	689 (56.8)	.95
Male	5209 (43.1)	523 (43.2)	
Income quintile			
1	2043 (16.9)	289 (23.8)	< .001
2	2291 (18.9)	230 (19.0)	
3	2334 (19.3)	215 (17.7)	
4	2551 (21.1)	237 (19.6)	
5	2826 (23.4)	236 (19.5)	
Rurality			
Urban	10 577 (87.4)	1026 (84.7)	.01
Rural	1510 (12.5)	186 (15.3)	
Liver disease[a]			
No	12 084 (99.9)	1197 (98.8)	< .001
Yes	14 (0.1)	15 (1.2)	
Alcohol use[b]			
No	11 808 (97.6)	1145 (94.5)	< .001
Yes	290 (2.4)	67 (5.5)	
Diabetes mellitus[c]			
No	8455 (69.9)	737 (60.8)	< .001
Yes	3643 (30.1)	475 (39.2)	
Renal dysfunction[b]			
No	11 467 (94.8)	1059 (87.4)	< .001
Yes	631 (5.2)	153 (12.6)	
No. of antidepressants,[b] mean ± SD	0.32 ± 0.64	0.56 ± 0.81	< .001
No. of opioids,[b] mean ± SD	0.49 ± 0.73	0.80 ± 0.95	< .001
No. of benzodiazepines,[b] mean ± SD	0.27 ± 0.52	0.40 ± 0.62	< .001
No. of antipsychotics,[b] mean ± SD	0.07 ± 0.30	0.12 ± 0.41	< .001
Charlson score			
0	1572 (13.0)	195 (16.1)	< .001
1	849 (7.0)	136 (11.2)	
2	518 (4.3)	110 (9.1)	
≥3	614 (5.1)	166 (13.7)	
No prior hospitalizations	8545 (70.6)	605 (49.9)	
No. of ED visits,[b] mean ± SD	0.97 ± 1.84	2.64 ± 3.24	< .001
No. of hospitalizations,[b] mean ± SD	0.22 ± 0.56	0.53 ± 0.93	< .001

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: ED, emergency department; SD, standard deviation.

[a]Diagnosed in the past 2 years.

[b]Diagnosed in the past year.

[c]Diagnosed in their lifetime.

following metronidazole use (0.25%) is on par with the incidence of other serious antibiotic-adverse events that have prompted warnings from the United States Food and Drug Administration [20]. Clinicians should report metronidazole-associated central and peripheral nervous system adverse events to federal health agencies.

Table 2. Association Between Metronidazole and Neurologic Adverse Events for Cases Compared to Controls[a]

Metronidazole (vs Clindamycin)	Unadjusted OR (95% CI)	Unadjusted *P* Value	Adjusted OR (95% CI)	Adjusted *P* Value
Primary outcome				
Central or peripheral nervous system events	1.72 (1.53–1.94)	< .001	1.43 (1.26–1.63)	< .001
Secondary outcomes				
Central nervous system events	1.76 (1.54–2.01)	< .001	1.46 (1.27–1.68)	< .001
Peripheral nervous system events	1.60 (1.25–2.05)	< .001	1.34 (1.02–1.76)	.036

Abbreviations: CI, confidence interval; OR, odds ratio.

In nearly 100 published reports of metronidazole-associated central and peripheral nervous system toxicity [6, 8], the distinctiveness of the clinical syndromes has strengthened the causal link with metronidazole. However, to our knowledge, this represents the first systematic assessment of this phenomenon at the population level. More rigorous epidemiologic tests of causality are unlikely given that most randomized controlled trials (RCTs) of metronidazole are neither large nor long enough to detect rare adverse events. One small RCT of metronidazole use as part of an empiric regimen for multidrug-resistant tuberculosis was terminated early due to high rates of peripheral neuropathy in the metronidazole arm (8/16 [50%]) [21]. Our incident cohort of metronidazole users suggests that the actual event rates of central and peripheral nervous system toxicity are likely orders of magnitude lower, 0.2% and 0.05%, respectively.

The pathogenesis of metronidazole-induced neurologic toxicity is not well understood, with most existing research from animal models. Metronidazole crosses the blood-brain barrier freely, achieving cerebrospinal fluid concentrations equal to serum levels [22]. In a rat model, metronidazole bound to CNS ribonucleic acid, inhibiting protein synthesis and triggering axonal degradation [22]. The administration of 800 mg/kg/day of metronidazole to rats over 6 weeks induced symmetrical lesions

Table 3. Association Between Metronidazole (as a Categorical Variable) and Neurologic Events for Cases Compared to Controls[a]

Metronidazole[a]	Unadjusted OR (95% CI)	Unadjusted *P* Value	Adjusted[b] OR (95% CI)	Adjusted[b] *P* Value
Low (< 9.9 g)	1.68 (1.43–1.98)	< .001	1.62 (1.37–1.92)	< .001
Medium (9.9–19.9 g)	1.54 (1.31–1.81)	< .001	1.22 (1.03–1.45)	.03
High (> 19.9 g)	2.25 (1.83–2.77)	< .001	1.56 (1.24–1.95)	< .001

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Reference = clindamycin.

[b]Models adjusted for demographics (income quintile and rurality), comorbidities (liver disease, alcohol use, diabetes mellitus, renal dysfunction, and Charlson score), concurrent medications (number of antidepressants, antipsychotics, benzodiazepines, and opioids), and healthcare utilization (number of emergency department visits and hospitalizations).

in vestibular, cochlear, and cerebellar nuclei [23]. One possible pathway involves γ-amino butyric acid receptor modulation [24]. Metronidazole-induced neuropathy may also relate to its ability to induce oxidation of norepinephrine, dopamine and other catecholamine derivatives to generate superoxide radicals, increasing water content and promoting axonal swelling [25]. It is not clear whether metronidazole-induced neurologic toxicity is an idiosyncratic or dose-dependent reaction. In one of the largest systematic reviews of prior case reports of CNS toxicity, the average cumulative dose of metronidazole was high (93.4 g) and the mean duration of treatment was prolonged (54 days) [6]. However, a large range of cumulative doses have been reported (0.25–1095 g), and 26% of cases developed with < 7 days of exposure, and 11% with < 3 days of exposure [6]. Similarly, the largest systematic review of metronidazole-induced peripheral neuropathy detected a higher risk of neuropathy at cumulative metronidazole doses exceeding 42 g [26]. The results of our case-control study do not indicate an obvious dose-dependence, and so it is possible that the prior case report literature is prone to publication bias—with more common reporting of cases detected after high cumulative exposures.

Strengths of our analysis include the use of population-wide datasets in a large jurisdiction with universal identification of prescriptions and healthcare encounters. Although the databases are well validated [17, 27], the operating characteristics of the *ICD-10* codes used to define our outcomes are unknown. We expect that we have likely undercaptured these neurologic outcomes, especially those that were mild enough to be treated entirely within an outpatient setting. Differential outcome ascertainment could have biased our results if clinicians were widely knowledgeable about this toxicity and more likely to identify these outcomes among metronidazole users. Our study is strengthened by the use of an active comparator drug, but we acknowledge the limitation that clindamycin indications are not identical to those of metronidazole. Finally, we only had access to drug exposure data for those > 65 years old, so our estimates of risk may not be generalizable to children and younger adults.

In summary, we found that central and peripheral nervous system adverse events were associated with an increased odds of metronidazole exposure relative to clindamycin. Metronidazole central and peripheral neurotoxicity is rare but potentially debilitating. Patients with concomitant liver disease, renal disease, alcohol use, and neurotropic medicine use are at particularly high risk for these complications. Clinicians and patients should be aware of these rare but serious adverse events, along with their potentially distinctive features.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. N. D. was involved in the conception of the study and wrote the first draft. Y. C. carried out the statistical analysis with J. G.'s support. All authors were involved in the design and planning of the study, participated in further drafts, and approved of the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. N. D. is the guarantor.

Acknowledgments. The authors thank IMS Brogan Inc for use of its Drug Information Database.

Disclaimer. The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES, the Ontario Ministry of Health and Long-Term Care (MOHLTC), or the Canadian Institutes of Health Research (CIHR) is intended or should be inferred. Parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, views, and conclusions reported in this work are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed in the material are those of the author(s), and not necessarily those of CIHI.

Financial support. This work was supported by a Project Grant from the CIHR (grant number PJT153117 to N. D.). This study was also supported by ICES, which is funded by an annual grant from MOHLTC.

Potential conflicts of interest. D. N. J. reports being an unpaid member of Physicians for Responsible Opioid Prescribing. He is also a member of the American College of Medical Toxicology and has received payment for lectures and medicolegal opinions regarding the safety and effectiveness of analgesics, including opioids. M. M. M. reports honoraria for advisory board meetings from NovoNordisk, Neurocrine, and Allergan, outside the submitted work. T. G. reports grant funds for a research program from the Ontario Ministry of Health, outside the submitted work. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Tally FP, Sutter VL, Finegold SM. Metronidazole versus anaerobes. In vitro data and initial clinical observations. Calif Med **1972**; 117:22–6.
2. Magill SS, Edwards JR, Beldavs ZG, et al; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Prevalence of antimicrobial use in US acute care hospitals, May-September 2011. JAMA **2014**; 312:1438–46.
3. Baggs J, Fridkin SK, Pollack LA, Srinivasan A, Jernigan JA. Estimating national trends in inpatient antibiotic use among US hospitals from 2006 to 2012. JAMA Intern Med **2016**; 176:1639–48.
4. Giannini AJ. Side effects of metronidazole. Am J Psychiatry **1977**; 134:329–30.
5. Patel K, Green-Hopkins I, Lu S, Tunkel AR. Cerebellar ataxia following prolonged use of metronidazole: case report and literature review. Int J Infect Dis **2008**; 12:e111–4.
6. Kuriyama A, Jackson JL, Doi A, Kamiya T. Metronidazole-induced central nervous system toxicity: a systematic review. Clin Neuropharmacol **2011**; 34:241–7.
7. Bottenberg MM, Hegge KA, Eastman DK, Kumar R. Metronidazole-induced encephalopathy: a case report and review of the literature. J Clin Pharmacol **2011**; 51:112–6.
8. Sarna JR, Furtado S, Brownell AK. Neurologic complications of metronidazole. Can J Neurol Sci **2013**; 40:768–76.
9. Kato H, Sosa H, Mori M, Kaneko T. Clinical characteristics of metronidazole-induced encephalopathy: a report of two cases and a review of 32 Japanese cases in the literature [in Japanese]. Kansenshogaku Zasshi **2015**; 89:559–66.
10. Roy U, Panwar A, Pandit A, Das SK, Joshi B. Clinical and neuroradiological spectrum of metronidazole induced encephalopathy: our experience and the review of literature. J Clin Diagn Res **2016**; 10:OE01–9.
11. Farmakiotis D, Zeluff B. Images in clinical medicine. Metronidazole-associated encephalopathy. N Engl J Med **2016**; 374:1465.
12. Sarna JR, Brownell AK, Furtado S. Cases: reversible cerebellar syndrome caused by metronidazole. CMAJ **2009**; 181:611–3.

13. Mamdani M, McNeely D, Evans G, et al. Impact of a fluoroquinolone restriction policy in an elderly population. Am J Med **2007**; 120:893–900.
14. Daneman N, Bronskill SE, Gruneir A, et al. Variability in antibiotic use across nursing homes and the risk of antibiotic-related adverse outcomes for individual residents. JAMA Intern Med **2015**; 175:1331–9.
15. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open **2015**; 5:e010077.
16. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med **2006**; 354:1352–61.
17. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario drug benefit database. Can J Clin Pharmacol **2003**; 10:67–71.
18. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with *ICD-9-CM* administrative databases. J Clin Epidemiol **1992**; 45:613–9.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
20. US Food and Drug Administration. FDA drug safety communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. **2016**. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-advises-restricting-fluoroquinolone-antibiotic-use-certain. Accessed 21 April 2020.
21. Carroll MW, Jeon D, Mountz JM, et al. Efficacy and safety of metronidazole for pulmonary multidrug-resistant tuberculosis. Antimicrob Agents Chemother **2013**; 57:3903–9.
22. Bradley WG, Karlsson IJ, Rassol CG. Metronidazole neuropathy. Br Med J **1977**; 2:610–1.
23. von Rogulja P, Kovac W, Schmid H. Metronidazole encephalopathy in rats [in German]. Acta Neuropathol **1973**; 25:36–45.
24. Evans J, Levesque D, Knowles K, Longshore R, Plummer S. Diazepam as a treatment for metronidazole toxicosis in dogs: a retrospective study of 21 cases. J Vet Intern Med **2003**; 17:304–10.
25. Rao DN, Mason RP. Generation of nitro radical anions of some 5-nitrofurans, 2- and 5-nitroimidazoles by norepinephrine, dopamine, and serotonin. A possible mechanism for neurotoxicity caused by nitroheterocyclic drugs. J Biol Chem **1987**; 262:11731–6.
26. Goolsby TA, Jakeman B, Gaynes RP. Clinical relevance of metronidazole and peripheral neuropathy: a systematic review of the literature. Int J Antimicrob Agents **2018**; 51:319–25.
27. Canadian Institute for Health Information (CIHI). National Ambulatory Care Reporting System CIHI data quality study of Ontario emergency department visits for 2004–2005: executive summary. Ottawa, Ontario, Canada: CIHI, **2007**.