Background
Chemotherapy-induced Nausea and Vomiting (CINV) is one of the most commonly experienced adverse drug effects experienced by cancer patients [1]. CINV is associated with deterioration in quality of life and has a significant impact on daily functioning [2] [3]. Uncontrolled CINV can result in nutritional deficits or anorexia, reduced self-care and functional ability, and can compromise adherence or lead to the withdrawal of potentially curative anticancer treatment [4].

In Canada, Cancer Care Ontario (CCO) and the British Columbia Cancer Agency (BCCA) each publish antiemetic guidelines. Both Canadian guidelines recommend, for patients receiving Moderately Emetogenic Chemotherapy (MEC) or Highly Emetogenic Chemotherapy (HEC), a combination of dexamethasone, one day of a 5-hydroxytryptamine 3 receptor antagonist (5-HT3 RA), with or without a neurokinin-1 receptor antagonist (NK1 RA) for the prevention of CINV [5] [6]. However, 20-30% of patients receiving MEC or HEC chemotherapy experience breakthrough nausea or vomiting despite using guideline-recommended antinausea regimens [7]. In an effort to control breakthrough CINV, physicians may be prescribing additional anti-emetic agents as opposed to following guideline-based therapy.

Results
A total of 318 5-HT3 RA prescriptions from 46 pharmacies were collected and analyzed (Figure 1). Of these, 49% were for cancer-related diagnoses (356/318). Within the prescriptions written and dispensed for cancer, ondansetron, granisetron, and palonosetron were the most frequently prescribed (85%, 132/156). The remaining prescriptions were for granisetron (12/156) and palonosetron (2/156) (Figure 2). The average total price charged by pharmacies, for each dispensable prescription, across all 5-HT3 RAs for cancer emesis was $112.18 (includes drug costs, mark-ups and dispensing fees); excluding prescriptions with duration of greater than 20 days, the average claim price was $81.88. For ondansetron specifically, 99% (131/132) was dispensed as generic ondansetron. The average claim price for ondansetron prescriptions was $102.92; excluding prescriptions with duration of greater than 20 days, the average claim price was $82.73.

For these prescriptions, 62% (96/156) were covered by public payers. The remaining prescriptions were covered by private payers (29%, 46/156) or self-paid (9%, 14/156). Across all 5-HT3 prescriptions written for cancer emesis, 37% (57/156) had instructions to be taken on as needed basis (PRN).

For ondansetron prescriptions, 92% (122/132) were dispensed as tablets, while the remaining prescriptions were dispensed as oral disintegrating tablets (ODT) or oral disintegrating film (ODF). When ondansetron tablets were prescribed, the most common dosing schedule was 8mg twice daily, the next most common were 8mg three times daily and 8mg once daily. A breakdown of ondansetron doses prescribed for cancer emesis can be found in Table 1. The average daily dose of ondansetron was 16.4mg, while for granisetron it was 3.1mg and for palonosetron it was 0.5mg (Table 2).

Discussion
5-HT3 RAs are widely available in Canada and listed on public and private formularies across the country. These treatments are used for both cancer (49%) and non-cancer (51%) emesis prevention. This study isolated 5-HT3 RA use amongst cancer patients only, and investigated real-world duration of therapy with ondansetron, granisetron, and palonosetron. It was found that 39% of 5-HT3 RAs given for cancer-related emesis were given for more than 5 days. With acute CINV defined as nausea or vomiting within the first 24 hours (day 1) and delayed CINV for 25-120 hours (days 2-5) after chemotherapy, this data suggests that physicians may be concerned about nausea or vomiting beyond acute and delayed CINV. A limitation of the study is that the cancer concurrent treatment received was not collected. Cancer-related emesis can occur for a variety of reasons not limited to chemotherapy-induced, including radiation therapy, or due to the cancer itself [8]. Further, patients may receive sequential chemotherapy regimens involving toxic drugs multiple times within a chemotherapy cycle, or may receive concurrent chemo-radiation therapy. Each of these situations may warrant a different level of emesis prevention.

Additionally, 37% of 5-HT3 RA prescriptions written for cancer patients had instructions to be given on an “as needed” basis. This suggests that physicians may be prescribing higher quantities of 5-HT3 RAs to allow for flexibility in dosing, so that patients have a sufficient supply in cases of ongoing delayed nausea or vomiting.

Previous research conducted by Cancer Care Ontario showed that after the introduction of aprepitant (an NK1 RA) and the 2013 update to their antinausea recommendations, there was good uptake to add aprepitant to a 5-HT3 RA, but no decline in 5-HT3 RA use despite the recommendation for 5-HT3 use only on Day 1 for both HEC and MEC. That research did not include dates on duration of 5-HT3 treatment at baseline or after the introduction of aprepitant, only that the number of HEC and MEC cases remained stable while both the cost and number of prescriptions for 5-HT3 RAs did change after the recommendations were updated. Recognizing that there are multiple uses of 5-HT3 RAs, the authors did not provide details on how they determined that Ontario Drug Benefits (ODB) expenditures were related to chemotherapy-induced emesis as opposed to other oncology or non-oncology uses for 5-HT3 RAs.

Conclusion
Our Real-World audit of 5-HT3 RA use found that, on average, even after excluding longer term use (>20 days), five days of a 5-HT3 RA was prescribed for cancer patients. Amongst prescriptions written for one to five days (period of acute and delayed CINV), 20% were written for 1 day, as per provincial and international antinausea guidelines. This data suggests physicians may have ongoing concerns about delayed nausea and vomiting prevention in cancer patients. These concerns could be addressed by the use of more effective and longer acting 5-HT3 RAs, as well as combination treatment with NK1 RAs for a broader set of chemotherapy regimens than those currently defined as NEC. This may lead to better adherence to duration guidelines with respect to 5-HT3 RA treatment duration. Further work is needed to understand the causes and management concerns for nausea and vomiting beyond 1 to 5-day period.

References

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