Potential drug interactions in patients with a history of cancer

L. Chen and W.Y. Cheung MD MPH*†*

ABSTRACT

Background

Cancer survivors (css) are frequently exposed to polypharmacy, which might increase their risk of drug interactions. Our study aimed to determine the relative prevalence of potential drug interactions (PDIS) among CSS compared with non-cancer respondents (NCRS).

Methods

Self-reported prescription data from 4975 patients were extracted from the U.S. National Health and Nutrition Examination Survey and screened for PDIS using iFacts: Drug Interaction Facts (Facts and Comparisons, St. Louis, MO, U.S.A.). The clinical significance of each PDI was graded on a 5-point scale based on the severity of the interaction and the level of evidence documenting the interaction. Summary statistics and logistic regression models were used to assess the impact of cancer history on the risk of PDIS.

Results

Of patients eligible for the analyses, the CSS ($n = 302$) indicated using 4.4 ± 0.22 prescriptions on average, and the NCRS ($n = 908$), 3.8 ± 0.09 . Nearly half of both cohorts (40% of CSS, 43% of NCRS) had at least 1 PDI. In both cohorts, 12% were at risk for fatal or permanently debilitating effects. In multivariate analyses, CSS were significantly less likely than NCRS to be at risk for any PDIS (odds ratio: 0.65; 95% confidence interval: 0.46 to 0.92; $p = 0.02$). Advanced age and low household income were associated with PDIS among CSS. Medications most commonly prescribed to CSS with a PDI included metoprolol (15.6%), levothyroxine (13.6%), and furosemide (11.9%).

Conclusions

Although CSS appear to be less susceptible than NCRS to PDIS, the prevalence of PDIS among CSS remains

suboptimal. Specific subgroups of CSS may be particularly prone to PDIS, underscoring the importance of increased vigilance.

KEY WORDS

Polypharmacy, potential drug interactions, prescription, survivors

1. INTRODUCTION

With the changing demographics of an aging population, polypharmacy has become an increasingly pertinent issue in clinical practice¹⁻⁶. In the literature, polypharmacy has been defined as the use of multiple drugs and of more drugs than clinically indicated. Despite the differences in definition, authors generally agree that the prevalence of polypharmacy has increased dramatically in recent decades and continues to increase¹⁻⁶. Analyses of nationally representative surveys from the Swedish Panel Study of Living Conditions of the Oldest Old found that polypharmacy rates more than doubled to 46% in 2002 from 18% in 1992⁶. Likewise, a large study of elderly subjects (≥ 65 years of age) in Italy demonstrated that 46% were exposed to polypharmacy⁷.

With the introduction of new and more complex medications, polypharmacy will become increasingly common, elevating the risk for potential drug interactions (PDIS)^{8,9}. Because the risk of drug interactions can vary significantly based on patient characteristics such as age^{4,7,10}, sex¹¹, and body composition⁴, and on medication characteristics such as the number and types of drugs being used^{7,9,12,13}, PDIS can be difficult to screen for and to detect, underscoring the need to develop ways of identifying high-risk individuals.

Several large studies have explored polypharmacy and PDIS in the general population^{6,7}, but a literature search yielded no studies making similar direct comparisons in cancer survivors (CSS) and non-cancer patients. Prior studies evaluating drug interactions in CSS have been relatively small^{9,14-16}, localized to single

centres or institutions^{14,15}, or unable to compare CSS with controls^{14–16}. Importantly, CSS constitute a patient group that is highly vulnerable to PDIS for several reasons. First, prior or ongoing anticancer treatments can result in side effects that limit the repertoire of drugs that might otherwise be considered safe and available in non-cancer patients^{9,12,17–19}. Second, many CSS are elderly, and altered drug metabolism in this age group might make them more susceptible to adverse drug interactions^{10,19,20}. Third, CSS frequently take concomitant prescription and over-the-counter (OTC) medications for the management of either other comorbidities or late toxicities from anticancer therapies^{9,17,19,21,22}. For instance, one U.S. study of CSS found that 96% consumed at least 1 prescription drug, and 71%, at least 1 OTC drug, 3 days before their chemotherapy²³. Another analysis observed that 2% of unplanned hospital visits by CSS were secondary to drug interactions²⁴. That finding likely underestimates the true frequency, because concomitant complaints and symptoms at the time of medical presentation might lead clinicians to attribute a hospital visit to a cause other than drug interaction. Despite those observations, only a few studies have directly compared the rate of PDIS in CSS and non-cancer patients.

2. METHODS

2.1 Data Source and Study Cohort

The data used in our analyses were acquired from the U.S. population-based National Health and Nutrition Examination Survey (NHANES). Specifically, NHANES is a cross-sectional, nationally representative survey conducted biennially in participants' homes in conjunction with well-equipped mobile medical centres designed to assess the health and nutrition status of adults in the United States. The survey consists of an in-person interview component that collects self-reported patient demographics, general health information, and socioeconomic and dietary status, and a clinical component that consists of medical, physiologic, and laboratory measurements taken by trained professionals. The NHANES has been approved by the U.S. National Center for Health Statistics and obtains informed consent from all participants. Our cohort was limited to participants 18–85 years of age at the time of the study. Respondents whose questionnaire reported ever having cancer were classified as CSS. They were compared with non-cancer respondents (NCRS) who denied having any history of a prior or current cancer diagnosis.

2.2 Study Inclusion Criteria

Prescriptions from the 2007–2008 NHANES were self-reported by participants and were included in the present analysis only if survey respondents

provided either the drug name or drug container to the examiner. Because the analysis used a screening program for PDIS, only patients with at least 2 recorded prescriptions recognized by our screening program were considered.

2.3 Definition of Polypharmacy and PDI

Participants in NHANES are specifically asked to describe all of their current prescription medications. For the purposes of our study, polypharmacy was considered to be the use of 2 or more prescription drugs. To screen for PDIS, the names of the medications self-reported by each respondent were manually entered into a specialized software program called iFacts: Drug Interaction Facts (version 13.10: Facts and Comparisons, St. Louis, MO, U.S.A.)^{15,23}. The iFacts program is designed to identify the presence of PDIS; it also evaluates the “significance” of all PDIS on a 5-point scale (Table 1), which takes into consideration the level of severity and the amount of scientific evidence supporting the specific interaction. The severity level was graded as major (effects could cause permanent damage or death), moderate (effects could worsen clinical status and potentially require intervention or hospitalization), or minor (effects, if any, are mild and generally will not require intervention). The evidence level was categorized into established (proven to occur in clinical studies), probable (very likely, but not yet clinically proven), suspected (supported by good data, but requires further study), possible (limited data, but could occur), or unlikely (possible, but lacks good supporting evidence).

2.4 Description of the Covariates

Demographic features and socioeconomic characteristics of CSS were compared with those of the NCRS. We analyzed various demographic features, including age, sex, ethnicity, and time lived in the United States. Specifically, age was dichotomized into less than or 60 or more years of age, and ethnicity was classified as Hispanic, non-Hispanic white, non-Hispanic black, and other races (including multiracial). Time lived in the United States was

TABLE 1 5-Point scale for potential significance of drug interaction

Significance	Severity	Level of evidence
1	Major	Suspected or more
2	Moderate	Suspected or more
3	Minor	Suspected or more
4	Major or moderate	Possible
5	Minor	Possible
	Any	Unlikely

categorized into less than 10 years, 10–30 years, and more than 30 years. Socioeconomic characteristics—marital status, highest educational attainment, and annual household income—were also evaluated in the analyses. Marital status was grouped into married or living with a partner, widowed, separated or divorced, and never married. Educational attainment was classified into less than high school, graduation from high school, college degree, and graduate level degree. Household income was categorized as less than \$20,000, \$20,000–\$74,999, and \$75,000 or more.

2.5 Statistical Considerations

All statistical analyses were performed using Stata 11.0 (StataCorp LP, College Station, TX, U.S.A.). Appropriate survey weighting algorithms provided by NHANES were applied to all of the univariate analyses and multivariate regression models to account for sampling errors, nonresponses, and the overall complex survey design. Trends reported in the present study are therefore statistically representative of the U.S. population.

Baseline characteristics are reported as weighted proportions for categorical variables and as weighted means for continuous variables. The chi-square and *t*-tests were used to test significance in univariate analyses. Multinomial logistic regression models were constructed, and odds ratios (ORs) and 95% confidence intervals (CIs) were used to describe how a prior or current diagnosis of cancer or other clinical characteristics were associated with the risk for each of the following outcomes: any PDI; an established PDI; and severe PDI. A *p* value of 0.05 was considered significant in all of our statistical comparisons. The Wald test was used in the regression models to derive global *p* values.

3. RESULTS

3.1 Baseline Characteristics of the Study Cohort

The 1210 NHANES participants eligible for the present study included 302 CSS (25.0%) and 908 NCRS (75.0%). The CSS tended to be slightly older (mean age: 70.2 years vs. 68.3 years for the NCRS, *p* = 0.03) and were more likely to be of white ethnicity (80.1% vs. 63.2%, *p* = 0.04). Otherwise, most members of both the CS and NCR groups were women (54.0% vs. 58.7%, *p* = 0.81), married (60.3% vs. 54.6%, *p* = 0.48), had not completed college (76.9% vs. 82.8%, *p* = 0.45), and earned more than \$20,000 annually (72.5% vs. 71.5%, *p* = 0.33). Table II summarizes additional details of the baseline characteristics of the CSS and NCRS.

3.2 Patterns of Polypharmacy and PDIs

The CS group reported a significantly higher mean number of prescriptions (4.4 vs. 3.8 for the NCR group,

p = 0.01, Table III), although the difference did not persist once both groups were controlled for other factors (*p* = 0.16, Table IV). Most of the study cohort did not have a PDI (57.5% for CSS vs. 55.3% for NCRS), but a fair number of patients still had a medication profile that posed a potential risk for interaction that ranked as high as grade 1 or 2 on the significance rating scale (grade 1: 15.6% CSS vs. 11.5% NCRS; grade 2: 13.9% CSS vs. 14.7% NCRS). However, the overall risk for these PDIs appeared to be similar for the CSS and NCRS (*p* = 0.43). Likewise, in terms of the severity of the potential interactions, a fair number were classified as major (13.0% CSS vs. 12.2% NCRS) or moderate (24.6% vs. 26.1%), although the distribution of severity was similar in the groups (*p* = 0.44).

3.3 Risk Factors Associated with Medication Use and Interactions

Table IV shows the factors associated with multiple drug use. Advanced age (≥ 60 years) was consistently correlated with a significantly higher odds of using 3–5 (OR: 2.21; 95% CI: 1.32 to 3.70) or more than 5 (OR: 2.12; 95% CI: 1.23 to 3.64) medications (*p* < 0.008). Conversely, the odds of using many prescription drugs was lower for individuals with high annual household incomes of \$75,000 or more (3–5 drugs: OR, 0.77; 95% CI, 0.47 to 1.25; >5 drugs: OR, 0.51; 95% CI, 0.25 to 1.02) and \$20,000–\$74,999 (3–5 drugs: OR, 0.65; 95% CI, 0.49 to 0.87; >5 drugs: OR, 0.67; 95% CI, 0.48 to 0.92) than for individuals having incomes of less than \$20,000 (*p* < 0.05). Other clinical characteristics, such as sex, ethnicity, marital status, educational attainment, and time lived in the United States, were not associated with an increased risk of polypharmacy (all *p* > 0.05).

Table V highlights the main findings from our multinomial logistic regression model evaluating the associations of a cancer diagnosis and other clinical factors with the presence of major (grades 1 and 2) or minor (grades 3–5) PDIs. When compared with individuals having no history of cancer, individuals with either a prior or a current cancer diagnosis showed a significant trend toward a lesser risk for any PDI (OR: 0.65; 95% CI: 0.46 to 0.92; *p* = 0.02). The trend persisted at a nonsignificant level for major (OR: 0.68; 95% CI: 0.40 to 1.16) and minor (OR: 0.71; 95% CI: 0.50 to 1.01) PDIs.

Use of multiple drugs showed a very strong associations with risk of a PDI (*p* < 0.0001). Compared with patients taking 2–3 prescriptions, those taking 4–5 prescriptions experienced higher odds of a PDI (major: OR, 6.09; 95% CI, 3.64 to 10.2; minor: OR, 3.67; 95% CI, 2.02 to 6.64). Patients taking more than 5 prescriptions were at even greater risk (major: OR, 46.7; 95% CI, 26.4 to 82.7; minor: OR, 17.3; 95% CI, 9.6 to 31.3). Other clinical characteristics, such as age, annual household income, sex, ethnicity, marital status, and educational attainment were not independently associated with any outcome (all *p* > 0.05).

TABLE II Baseline characteristics of cancer survivors and non-cancer respondents

<i>Characteristic</i>	<i>Respondents</i>			<i>p Value</i>
	<i>Overall</i>	<i>Cancer survivors</i>	<i>Non-cancer respondents</i>	
Participants [<i>n</i> (%)]	1210 (100)	302 (25.0)	908 (75.0)	
Mean age (years)	68.8	70.2	68.3	0.032
Sex [<i>n</i> (%)]				0.813
Men	514 (42.5)	139 (46.0)	375 (41.3)	
Women	696 (57.5)	163 (54.0)	533 (58.7)	
Ethnicity [<i>n</i> (%)]				0.037
Hispanic	129 (10.7)	9 (3.0)	120 (13.2)	
Non-Hispanic white	816 (67.4)	242 (80.1)	574 (63.2)	
Non-Hispanic black	231 (19.1)	44 (14.6)	187 (20.6)	
Other, including multiracial	34 (2.8)	7 (2.3)	27 (3.0)	
Highest education level [<i>n</i> (%)]				0.451
High school				
Incomplete or lower	362 (30.0)	76 (25.2)	286 (31.5)	
Graduate, GED, or equivalent	335 (27.7)	79 (26.2)	256 (28.2)	
Some college or AA degree	287 (23.7)	77 (25.5)	210 (23.1)	
College graduate or higher	225 (18.6)	69 (22.8)	156 (17.2)	
Refused or don't know	1 (0.1)	1 (0.3)	0 (0.0)	
Annual household income [<i>n</i> (%)]				0.326
Under \$20,000	306 (25.3)	73 (24.2)	233 (25.7)	
\$20,000–\$74,999	656 (54.2)	170 (56.3)	486 (53.5)	
\$75,000+	212 (17.5)	49 (16.2)	163 (18.0)	
Unknown	36 (3.0)	10 (3.3)	26 (2.9)	
Marital status [<i>n</i> (%)]				0.481
Married or living with partner	678 (56.0)	182 (60.3)	496 (54.6)	
Widowed	294 (24.3)	68 (22.5)	226 (24.9)	
Divorced or separated	187 (15.5)	44 (14.6)	143 (15.7)	
Never married	51 (4.2)	8 (2.6)	43 (4.7)	
Unknown or refused	0 (0.0)	0 (0.0)	0 (0.0)	

GED = general educational development; AA = associate.

3.4 Most Frequently Prescribed Drugs for Patients with PDIs

Of the 10 drugs most frequently prescribed to CSS with PDIs, 9 were also among the 10 drugs most frequently prescribed to NCRS (Table VI). Those drugs included metoprolol, levothyroxine, furosemide, atorvastatin, warfarin, simvastatin, lisinopril, amlodipine, and hydrochlorothiazide. The medications most commonly prescribed to CSS with PDI were metoprolol (9.9%), levothyroxine (8.7%), and furosemide (7.6%).

4. DISCUSSION

In the present study, we hypothesized that data from NHANES 2007–2008 would show CSS to be at greater risk for PDIs because they are more inclined to take a higher number of cancer-related and non-cancer-related medications. On the contrary, we found that CSS were not at any higher risk than their non-cancer counterparts. In our univariate analyses, CSS showed similar levels of PDIs despite reporting significantly

TABLE III Mean prescriptions and distribution of potential drug interactions

<i>Variable</i>	<i>Respondents</i>			<i>p Value</i>
	<i>Overall</i>	<i>Cancer survivors</i>	<i>Non-cancer patients</i>	
Prescriptions				
Mean (<i>n</i>)	3.95	4.4	3.8	0.01
Number [<i>n</i> (%)]				0.43
1	170 (11.6)	47 (15.6)	123 (11.5)	
2	188 (14.5)	42 (13.9)	146 (14.7)	
3	22 (1.9)	2 (0.7)	20 (2.4)	
4	141 (12.1)	38 (12.6)	103 (12.0)	
5	25 (1.8)	6 (2.0)	19 (1.8)	
Interactions				
None [<i>n</i> (%)]	664 (58.1)	167 (55.3)	497 (57.5)	
Severity [<i>n</i> (%)]				0.44
Major	176 (12.4)	49 (13.0)	127 (12.2)	
Moderate	322 (25.7)	77 (24.6)	245 (26.1)	
Minor	48 (3.7)	9 (2.4)	39 (4.2)	
None evident	664 (58.1)	167 (60.0)	497 (57.5)	

TABLE IV Factors associated with polypharmacy

Characteristic	p Value	Use of multiple prescriptions			
		3–5 vs. 2–3		>5 vs. 2–4	
		OR	95% CI	OR	95% CI
Age	<0.008				
<60		Reference		Reference	
≥60		2.21	1.32 to 3.70	2.12	1.23 to 3.64
Cancer status	0.163				
Non-cancer patient		Reference		Reference	
Cancer survivor		0.98	0.64 to 1.49	1.40	0.96 to 2.03
Sex	0.649				
Men		0.97	0.72 to 1.32	1.13	0.83 to 1.54
Women		Reference		Reference	
Ethnicity	0.563				
Hispanic		Reference		Reference	
Non-Hispanic white		1.00	0.47 to 2.17	1.17	0.47 to 2.95
Non-Hispanic black		1.04	0.48 to 2.28	1.50	0.53 to 4.30
Other		2.41	0.94 to 6.17	2.55	0.84 to 7.75
Education	0.259				
High school					
Incomplete or lower		Reference		Reference	
Graduate, GED, or equivalent		0.99	0.63 to 1.54	1.25	0.86 to 1.81
College or AA degree		1.01	0.75 to 1.34	1.36	1.00 to 1.86
College graduate or higher		1.03	0.61 to 1.73	0.95	0.45 to 1.99
Annual household income	0.057				
<\$20,000		Reference		Reference	
\$20,000–\$74,999		0.65	0.49 to 0.87	0.67	0.48 to 0.92
≥\$75,000		0.77	0.47 to 1.25	0.51	0.25 to 1.02
Marital status	0.497				
Married or living with partner		Reference		Reference	
Widowed		1.05	0.64 to 1.72	1.05	0.65 to 1.68
Divorced or separated		1.14	0.70 to 1.88	1.31	0.68 to 2.51
Never married		3.80	1.21 to 11.88	3.22	0.99 to 10.42

GED = general educational development; AA = associate.

more prescriptions. Our multivariate model further demonstrated that cancer status was not independently associated with polypharmacy; rather, a prior cancer history was independently correlated with a reduced risk of both major and minor PDI.

These unexpected findings might in part be attributable to the emerging multi- and interdisciplinary nature of cancer care in the United States, in which cancer centres often have highly integrated health care teams that provide channels for close communication between oncologists, pharmacists, and family physicians. This type of practice setting has been demonstrated to improve the management of concomitant medications for patients^{25–27}. Because of the severity of the toxicities that can result from many cancer treatments, cancer care providers might also be more vigilant in evaluating medication histories for CSS and thus more inclined to actively

screen for PDIS on a regular basis than during the management of non-cancer patients^{28,29}.

The risk of PDIS was not particularly elevated among CSS compared with NCRS, but the absolute prevalence of PDIS remains suboptimal in both groups of patients (44.7% and 42.5% respectively). Additionally, the prevalence of PDIS that are associated with permanent, debilitating, or fatal side effects was 13.0% for CSS and 12.2% for NCRS. Our results showed that elderly patients (≥60 years of age as an independent risk factor) were not particularly susceptible to PDIS; however, they were highly exposed to polypharmacy. Because polypharmacy was the strongest predictor for increased risk of PDI in our analysis, we suggest that the high exposure of older patients to drug interactions can largely be attributed to the number of drugs they take. Indeed, one of our more alarming findings was that patients taking more

TABLE V Factors associated with major and minor potential drug interactions

Characteristic	p Value	Significance of interaction			
		Major vs. none		Minor vs. none	
		OR	95% CI	OR	95% CI
Age	0.863				
<60		Reference		Reference	
≥60		1.05	0.74 to 1.49	1.14	0.64 to 2.05
Cancer status	0.070				
Non-cancer patient		Reference		Reference	
Cancer survivor		0.68	0.40 to 1.16	0.71	0.50 to 1.01
Sex	0.162				
Men		0.79	0.55 to 1.16	1.16	0.77 to 1.75
Women		Reference		Reference	
Ethnicity	0.317				
Hispanic		Reference		Reference	
Non-Hispanic white		1.05	0.35 to 3.19	1.54	0.61 to 3.90
Non-Hispanic black		1.00	0.33 to 3.09	1.28	0.47 to 3.49
Other ethnicity		0.41	0.07 to 2.31	0.92	0.22 to 3.78
Education	0.521				
High school					
Incomplete or lower		Reference		Reference	
Graduate, GED, or equivalent		0.79	0.58 to 1.08	0.84	0.46 to 1.55
College or AA degree		0.92	0.57 to 1.46	0.71	0.27 to 1.89
College graduate or higher		0.96	0.49 to 1.86	0.89	0.31 to 2.56
Annual household income	0.183				
<\$20,000		Reference		Reference	
\$20,000-\$74,999		0.90	0.62 to 1.32	0.78	0.54 to 1.11
≥\$75,000		0.63	0.35 to 1.11	0.51	0.29 to 0.91
Marital status	0.611				
Married or living with partner		Reference		Reference	
Widowed		1.27	0.81 to 1.99	0.93	0.57 to 1.49
Divorced or separated		0.57	0.26 to 1.26	0.45	0.17 to 1.21
Never married		0.90	0.25 to 3.16	1.29	0.35 to 4.72
Multiple prescriptions	<0.0001				
2–3		Reference		Reference	
4–5		6.09	3.64 to 10.19	3.67	2.02 to 6.64
>5		46.72	26.39 to 82.71	17.3	9.59 to 31.25

^a Grades 1 and 2.^b Grades 3 to 5.

OR = odds ratio; CI = confidence interval; GED = general educational development; AA = associate.

than 5 prescriptions had odds for being exposed to a PDI that was higher by a factor of 47 compared to patients taking 2–3 prescriptions. Those findings corroborate results in another study in geriatric CSS (70–90 years of age), which found that patients were taking an average of 9.1 prescriptions³⁰. As the U.S. population continues to age, the number of elderly patients who will be diagnosed with cancer is expected to steadily increase, thus making polypharmacy and PDIs particularly pertinent issues in the care of future CSS.

Our analyses also revealed that a high annual household income was associated with a decreased

risk of polypharmacy. Although a number of studies have explored the role of medical and socioeconomic factors and their effects on medication use and adherence, the impact of income on polypharmacy has not been as well described in the literature. One of the few studies in the area found that poor income levels were associated with lower self-perceived health and more comorbidities³¹. That association might be one possible explanation for the association of more prescriptions with lower income in our study cohort.

Many earlier studies showed an increased susceptibility of CSS to drug interactions and polypharmacy. Those studies frequently found that CSS

TABLE VI Prevalence of medications among respondents with potential drug–drug interactions

Rank	Respondent group			
	Cancer survivors		Non-cancer patients	
	Drug	[n (%)]	Drug	[n (%)]
1	Metoprolol	49 (15.6)	Metoprolol	128 (14.1)
2	Levothyroxine	41 (13.6)	Hydrochlorothiazide	125 (13.8)
3	Furosemide	36 (11.9)	Levothyroxine	106 (11.7)
4	Atorvastatin	32 (10.6)	Atorvastatin	97 (10.7)
5	Warfarin	31 (10.3)	Simvastatin	92 (10.1)
6	Simvastatin	30 (9.9)	Furosemide	84 (9.25)
7	Lisinopril	30 (9.9)	Lisinopril	81 (8.9)
8	Amlodipine	27 (8.9)	Metformin	72 (7.9)
9	Hydrochlorothiazide	26 (8.6)	Amlodipine	69 (7.6)
10	Atenolol	21 (7.0)	Warfarin	58 (6.4)

were older, more likely to report taking multiple concomitant medications to treat cancer and its associated symptoms, and more inclined to experience greater treatment-induced toxicities and more comorbid conditions. One such study screened hospitalized cancer patients and detected 180 potential drug interactions in 63% of its patients¹⁵. However, almost all of the studies were descriptive in nature and did not specifically compare rates of interactions and polypharmacy with those observed in a similar non-cancer population. Thus, one of the strengths of the present analysis is its comparisons of medication profiles in CSS and NCRS participating in NHANES, which is weighted in such a manner that results are representative of the U.S. population.

Medication profiles for the respondents included in our study who were at high risk for PDIS were similar in the CSS and NCRS: 9 of the 10 drugs most commonly implicated for a PDI in CSS were also among the drugs most frequently prescribed to NCRS. The most prominent category of drugs included those prescribed for treatment of hypertension, angina, and peripheral edema (for example, metoprolol, lisinopril, amlodipine, furosemide, and hydrochlorothiazide)—a finding that is expected, given that those medications represent drugs that are very commonly used in the general population. Statins—including atorvastatin and simvastatin—are another class of drugs heavily implicated in potential interactions. We also observed that warfarin was most frequently associated with potential interactions of the greatest severity. That finding is not surprising, given that warfarin is a potent anticoagulant and that many drugs can affect its absorption or metabolism. Our list of offending drugs (Table VI) should be considered by physicians so that they can be vigilant about PDIS whenever those drugs are prescribed to their patients.

Our study has several limitations. First, NHANES included only self-reported prescriptions or prescriptions

for which labelled bottles were provided to survey staff, which might have biased the survey toward underreporting of specific prescriptions. Furthermore, herbal products and OTC medications were not collected, and so we could not reliably describe or analyze potential interactions that involve those classes of drugs. Moreover, our analysis exploring PDIS used data from a cross-sectional survey within a particular time period. We therefore cannot comment on temporal patterns in PDIS. Future studies should investigate how medication patterns and polypharmacy might be changing over time. Finally, PDIS might not actually represent medication interactions that truly require medical attention. However, PDIS are admittedly difficult to study because serious adverse events from drugs are typically rare, thus necessitating assembly of a large longitudinal cohort.

5. CONCLUSIONS

Our study demonstrated that polypharmacy and PDIS remain prevalent problems for both CSS and NCRS. To better manage concomitant medications in these two patient populations, Sokol *et al.*³⁰ offered these recommendations:

- routine reassessment of all prescriptions, OTCs, and herbal products; and
- communication of a complete list of medications between health care providers on every referral, hospital admission, hospital transfer, and hospital discharge.

Similar suggestions and guidelines have been proposed by geriatric and supportive care associations^{27,28,32–37}. For those reasons, a concerted effort should be made to incorporate those recommendations into routine clinical practice for both CSS and elderly patients in general.

6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to disclose.

7. REFERENCES

1. Moen J, Norrgård S, Antonov K, Nilsson JL, Ring L. GPS' perceptions of multiple-medicine use in older patients. *J Eval Clin Pract J Eval Clin Pract* 2010;16:69–75.
2. Maggiore RJ, Gross CP, Hurria A. Polypharmacy in older adults with cancer. *Oncologist* 2010;15:507–22.
3. Hoffman DA, Schiller M, Greenblatt JM, Iosifescu DV. Polypharmacy or medication washout: an old tool revisited. *Neuropsychiatr Dis Treat* 2011;7:639–48.
4. He X, Clarke SJ, McLachlan AJ. Clinical pharmacology of chemotherapy agents in older people with cancer. *Curr Gerontol Geriatr Res* 2011;2011:628670.
5. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother* 2007;5:345–51.
6. Haider SI, Johnell K, Thorslund M, Fastbom J. Trends in polypharmacy and potential drug–drug interactions across educational groups in elderly patients in Sweden for the period 1992–2002. *Int J Clin Pharmacol Ther* 2007;45:643–53.
7. Nobili A, Franchi C, Pasina L, et al. Drug utilization and polypharmacy in an Italian elderly population: the EPIFARM–Elderly Project. *Pharmacoepidemiol Drug* 2011;20:488–96.
8. Tamura BK, Bell CL, Lubimir K, Iwasaki WN, Ziegler LA, Masaki KH. Physician intervention for medication reduction in a nursing home: the polypharmacy outcomes project. *J Am Med Dir Assoc* 2011;12:326–30.
9. Riechelmann RP, Tannock IF, Wang L, Saad ED, Taback NA, Krzyzanowska MK. Potential drug interactions and duplicate prescriptions among cancer patients. *J Natl Cancer Inst* 2007;99:592–600.
10. Boparai MK, Korc–Grodzicki B. Prescribing for older adults. *Mt Sinai J Med* 2011;78:613–26.
11. Venturini CD, Engroff P, Ely LS, et al. Gender differences, polypharmacy, and potential pharmacological interactions in the elderly. *Clinics (Sao Paulo)* 2011;66:1867–72.
12. Gridelli C. Same old story? Do we need to modify our supportive care treatment of elderly cancer patients? Focus on antiemetics. *Drugs Aging* 2004;21:825–32.
13. Magro L, Moretti U, Leone R. Epidemiology and characteristics of adverse drug reactions caused by drug–drug interactions. *Expert Opin Drug Saf* 2012;11:83–94.
14. Puts MT, Costa–Lima B, Monette J, et al. Medication problems in older, newly diagnosed cancer patients in Canada: how common are they? A prospective pilot study. *Drugs Aging* 2009;26:519–36.
15. Riechelmann RP, Moreira F, Smaletz O, Saad ED. Potential for drug interactions in hospitalized cancer patients. *Cancer Chemother Pharmacol* 2005;56:286–90.
16. van Leeuwen RW, Swart EL, Boven E, Boom FA, Schuitmaker MG, Hugtenburg JG. Potential drug interactions in cancer therapy: a prevalence study using an advanced screening method. *Ann Oncol* 2011;22:2334–41.
17. Beijnen JH, Schellens JH. Drug interactions in oncology. *Lancet Oncol* 2004;5:489–96.
18. Chan A, Ng TR, Yap KY. Clinically-relevant anticancer–antidepressant drug interactions. *Expert Opin Drug Metab Toxicol* 2012;8:173–99.
19. Repetto É. Greater risks of chemotherapy toxicity in elderly patients with cancer. *J Support Oncol* 2003;1(suppl 2):18–24.
20. Wilkinson GR. Drug metabolism and variability among patients in drug response. *N Engl J Med* 2005;352:2211–21.
21. van Leeuwen RW, Swart EL, Boom FA, Schuitmaker MS, Hugtenburg JG. Potential drug interactions and duplicate prescriptions among ambulatory cancer patients: a prevalence study using an advanced screening method. *BMC Cancer* 2010;10:679.
22. Werneke U, Earl J, Seydel C, Horn O, Crichton P, Fannon D. Potential health risks of complementary alternative medicines in cancer patients. *Br J Cancer* 2004;90:408–13.
23. Barrons R. Evaluation of personal digital assistant software for drug interactions. *Am J Health Syst Pharm* 2004;61:380–5.
24. Riechelmann RP, Del Giglio A. Drug interactions in oncology: how common are they? *Ann Oncol* 2009;20:1907–12.
25. Lees J, Chan A. Polypharmacy in elderly patients with cancer: clinical implications and management. *Lancet Oncol* 2011;12:1249–57.
26. Crotty M, Rowett D, Spurling L, Giles LC, Phillips PA. Does the addition of a pharmacist transition coordinator improve evidence-based medication management and health outcomes in older adults moving from the hospital to a long-term care facility? Results of a randomized, controlled trial. *Am J Geriatr Pharmacother* 2004;2:257–64.
27. Gokula M, Holmes HM. Tools to reduce polypharmacy. *Clin Geriatr Med* 2012;28:323–41.
28. Edwards BK, Howe HL, Ries LA, et al. Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on U.S. cancer burden. *Cancer* 2002;94:2766–92.
29. Blower P, de Wit R, Goodin S, Aapro M. Drug–drug interactions in oncology: why are they important and can they be minimized? *Crit Rev Oncol Hematol* 2005;55:117–42.
30. Sokol KC, Knudsen JF, Li MM. Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management. *J Clin Pharm Ther* 2007;32:169–75.
31. Kennedy BP, Kawachi I, Glass R, Prothrow–Stith D. Income distribution, socioeconomic status, and self rated health in the United States: multilevel analysis. *BMJ* 1998;317:917–21.
32. Browner IS, Ewachiw BD, Basile DA. Polypharmacy: managing chemotherapy in the older cancer patient with multiple comorbid conditions. Fort Washington, PA: NCCN Clinical Practice Oncology Forum; 2008. [Available online at: <http://www.medscape.org/viewarticle/580628>; cited November 5, 2012]
33. Schuling J, Gebben H, Veehof LJ, Haaijer–Ruskamp FM. Deprescribing medication in very elderly patients with multimorbidity: the view of Dutch GPs. A qualitative study. *BMC Fam Pract* 2012;13:56.
34. Ballentine NH. Polypharmacy in the elderly: maximizing benefit, minimizing harm. *Crit Care Nurs Q* 2008;31:40–5.
35. Hughes LD, McMurdo ME, Guthrie B. Guidelines for people not for diseases: the challenges of applying U.K. clinical guidelines to people with multimorbidity. *Age Ageing* 2013;42:62–9.

36. Rochon PA, Gurwitz JH. Prescribing for seniors: neither too much nor too little. *JAMA* 1999;282:113–15.
37. Schmader KE, Hanlon JT, Pieper CF, *et al.* Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. *Am J Med* 2004;116:394–401.

Correspondence to: Winson Y. Cheung, BC Cancer Agency, 600 West 10th Avenue, Room 4415, Vancouver, British Columbia V5Z 4E6.

E-mail: wcheung@bccancer.bc.ca

* University of British Columbia, Vancouver, BC.

† Division of Medical Oncology, BC Cancer Agency, Vancouver, BC.