

Utilization Pattern of Psychotropic Drugs in Oncology and Cardiology Ward in a Teaching Hospital in Malaysia

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ABSTRACT

This article examined the pattern of psychotropic drugs used among the hospitalized patients in oncology and cardiology wards in a Malaysia teaching hospital. Prescription records in the oncology and cardiology wards of University Malaya Medical Centre between 1st of January and 31st of December 2014 were obtained retrospectively from the pharmacy database. The main outcome was prescribing pattern, calculated as the total defined daily dose (DDD) for that group of drugs divided by the number of beds multiplied with 365 days. 11.8% (n=160) of patients in the oncology ward and 5.3% (n=168) of patients in the cardiology ward had prescription records of psychotropic drugs. The odds of patients prescribed with psychotropic drug in the oncology ward were significantly higher than patients in the cardiology ward (OR=2.37, 95%CI: 1.89-2.98). However, psychotropic drugs usage in cardiology ward (DDD per 100 bed-days = 92.53) was higher than oncology ward (DDD per 100 bed-days = 62.56). Oncology patients were more often prescribed with psychotropic drugs. However, it was 1.5-fold higher in the usage of psychotropic drugs in cardiology based on the DDD calculation. Hence, to initiate early treatment and psychological distress screening among the cancer and cardiology patients is crucial.

INTRODUCTION

Psychotropic drugs are defined as group of agents capable of modifying psychological function which results in alteration in behavior, emotion and consciousness. Psychological distress is largely defined as a state of emotional suffering characterized by symptoms of depression and anxiety. Psychological distress has been reported as high as 14% up to 50% among cancer patients particularly among those who required palliative care (Mhaidat *et al.*, 2009; Walker, *et al.*, 2013). Similarly, 24% of adults with severe cardiac conditions such as myocardial infarction appeared to suffer from depression

(Thombs *et al.*, 2006). A large population-based survey involving 10,641 patients discovered that the prevalence of major depression in cancer patients and heart failure patients were approximately two times higher than those who are absence of both diseases (Wilhelm *et al.*, 2003). More than 30% of cancer patients were presumed to suffer from depression during the final 24 hours of life death (Janberidze *et al.*, 2015).

The severity of psychological distress was reflected by an average of two psychotropic drugs per patient per prescription among cancer patients during hospitalization. Drug utilization reports of psychotropic drugs may reflect the detection of psychological distress or utilization of psychiatric services. In a previous study using the AGIS Health database, the authors demonstrated that psychotropic prescription rate were significantly higher among the cancer patients (Ng *et al.*, 2013).

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Subsequently, a retrospective cohort study utilizing a 5 years of pharmacy record showed that cancer patients were more often prescribed with any psychotropic drugs as compared to cardiology patients (Ng *et al.*, 2014). However, in both studies, the results were purely based on the prescription rate. The utilization of psychotropic drugs was not well-reflected by rate of prescriptions.

The dosage and duration of prescription and type of psychotropic drugs were not determined in either study. A variation of dosage could have been prescribed to treat psychological distress among these two groups of patients; hence it is difficult to identify the drug utilization between different therapeutic groups of psychotropic drugs. To overcome these limitations, we employ the Anatomical Therapeutic Chemical (ATC) code and Defined Daily Dose (DDD) system developed by the World Health Organization to conduct this study (World Health Organization, 2015).

This study aims to explore the psychotropic drugs which correspond to the third level of the ATC classification system called antipsychotics (N05A) anxiolytics (N05B), hypnotics and sedatives (N05C) and antidepressants (N06A). Using ATC/DDD system, this study will explore into total drug dosage and postulate amount of psychotropic drugs utilized for every patient within a certain time frame. This study will also use the Drug Utilization 90% (DU90%) method to illustrate the most commonly prescribed psychotropic drug and compare its drug prescribing pattern between cancer patients and patients with cardiovascular disease (Bergman *et al.*, 1998).

METHOD

Study Design and Sample

This hospital-based cross-sectional retrospective study was conducted at University Malaya Medical Centre (UMMC), teaching hospital, which is located in Kuala Lumpur, Malaysia. The study population includes all patients who were admitted in the 21-bed oncology ward and 39-bed cardiology ward in UMMC. Hospitalized patients in these two wards for the period January to December 2014 were screened and those who received at least one psychotropic drug during their stay were included in this study. This is a retrospective cohort study. This study was initiated with approval from Medical Ethics Committee of UMMC and registered with the National Medical Research Register (NMRR-15-2323-28496).

Prescription records of the study population dated between January 1, 2014 and December 31, 2014 were extracted using IBM's Cognos Business Intelligence PowerPlay from the Medication Management and Use System Ascribe (Version 10.09) database. Diagnosis and indication of the medications prescribed to patients could not be obtained from this database.

The main outcome

Psychotropic drugs in this study were operationally defined as the commonly used drugs for the treatment of

psychological distress. The total daily defined dose was calculated for psychotropic drugs with the following British National Formulary (BNF) codes; antipsychotics (BNF code 4.02), anxiolytics (BNF code 4.01.02), hypnotics (BNF code 4.01.01) and antidepressants (BNF code 4.03). These psychotropic drugs were assigned with their respective ATC codes in accordance to WHO Collaborating Centre for Drug Statistics Methodology (World Health Organization, 2015) and were aggregated into three broad therapeutic groups: N05A as antipsychotics, N05B and N05C as anxiolytics and N06A as antidepressants. Rate of drug utilization was calculated by combining the dose for each psychotropic drug and the dividing by the *ddd* (assigned by ATC/DDD system), number of beds and 365 days.

$$\text{DDD per 100 bed days} = \left(\frac{T}{\text{ddd} \times \text{No. of beds} \times 365 \text{ days}} \right) \times 100$$

The DDD per 100 bed days of psychotropic drugs in the same therapeutic group was summed together to yield a figure for that specific therapeutic group. This measurement is an estimate of prescribing rate of psychotropic drugs. All psychotropic drugs encountered in this study were arranged in a descending rank order of DDD per 100 bed days in a bar chart. A vertical broken line was used to indicate the sum of DDD per 100 bed days of drugs from the highest rank to lower rank that represent the 90% of the combined DDD per 100 bed days of all the drugs listed. The DU90% segment in the oncology ward and cardiology ward was compared. Drugs which appeared in the DU90% segment of the graph were interpreted as the most frequently used psychotropic drugs among cancer patients and patients with cardiovascular diseases.

Statistical Analysis

Prevalence of patients who received psychotropic drugs was compared between oncology and cardiology wards using odds ratio and 95% confidence interval (CI). Frequency tables were made to describe demographic variables and prescription pattern of the study population. Mean and standard deviation were calculated for continuous variables, whereas frequency and percentage were calculated for categorical variables. Intergroup comparisons were made using chi-squared test for gender, age group and ethnicity. Independent t-test was used to compare patients' age between groups. The comparisons were evaluated using two-sided significance level of 0.05.

Psychotropic monotherapy was defined as prescription records having one therapeutic group of psychotropic drugs whereas polypharmacy was defined as prescription records across two or more therapeutic groups within the study period. Patients on monotherapy were analyzed using logistic regression. Statistical Package for the Social Sciences (SPSS version 22, IBM Corporation) was used to perform all statistical analyses.

RESULTS

Table 1 showed the characteristic of patients in oncology and cardiology wards. Table 2 showed the 26 types of psychotropic drugs that were prescribed in the two wards. A total 11.8% (n=160) and 5.3% (n=168) patients in the oncology and cardiology wards respectively were prescribed with at least one psychotropic drugs.

Table 1: Characteristics of patients prescribed with psychotropic drug in oncology and cardiology wards.

Variable	Oncology Ward N=160 n (%)	Cardiology Ward N= 168 n (%)	p-value
Gender			
Female	117 (73.1)	77 (45.8)	p < 0.001*
Male	43 (26.9)	91 (54.2)	
Age group			
< 44 years	18 (11.2)	22 (13.1)	p < 0.001*
45 - 54 years	32 (20.0)	29 (17.3)	
55 - 64 years	55 (34.4)	41 (24.4)	
65 - 74 years	47 (29.4)	40 (23.8)	
75 years and above	8 (5.0)	36 (21.4)	
Mean age, years (SD)	59.02 (11.13)	61.43 (14.90)	p < 0.001 [#]
Ethnic			
Malay	27 (16.9)	45 (26.8)	p < 0.001*
Chinese	113 (70.6)	54 (32.1)	
Indian	18 (11.3)	66 (39.3)	
Others	2 (1.2)	3 (1.8)	

*Chi-squared test, [#]Independent t-test

Table 2: List of psychotropic drugs encountered in this study.

Therapeutic Group	ATC code	Drug Name	Oncology Ward	Cardiology Ward
Antipsychotics	1 N05AA01	Chlorpromazine	✓	✓
	2 N05AB03	Perphenazine	✓	✓
	3 N05AB04	Prochlorperazine	✓	✓
	4 N05AD01	Haloperidol	✓	✓
	5 N05AF01	Flupentixol	✓	✓
	6 N05AH02	Clozapine	✓	✓
	7 N05AH03	Olanzapine	✓	✓
	8 N05AH04	Quetapine	✓	✓
	9 N05AH05	Asenapine	✓	✓
	10 N05AL01	Sulpiride	✓	✓
	11 N05AN01	Lithium Carbonate	✓	✓
	12 N05AX08	Risperidone	✓	✓
	13 N05AX12	Aripiprazole	✓	✓
Anxiolytics, hypnotics and sedatives	1 N05BA01	Diazepam	✓	✓
	2 N05BA06	Lorazepam	✓	✓
	3 N05BA12	Alprazolam	✓	✓
	4 N05CD08	Midazolam	✓	✓
	5 N05CF02	Zolpidem	✓	✓
Antidepressants	1 N06AA02	Imipramine	✓	✓
	2 N06AA09	Amitriptyline	✓	✓
	3 N06AA16	Dosulepin	✓	✓
	4 N06AB03	Fluoxetine	✓	✓
	5 N06AB06	Sertraline	✓	✓
	6 N06AB10	Escitalopram	✓	✓
	7 N06AX03	Mianserin	✓	✓
	8 N06AX11	Mirtazapine	✓	✓

The odds of patients having a prescription record of psychotropic drug in the oncology ward were significantly higher

than patients in the cardiology ward (OR = 2.37, 95%CI: 1.89 – 2.98). Higher numbers of female and Chinese ethnicity in the oncology ward was prescribed with psychotropic drugs as compared to cardiology ward. However, they were significantly younger than patients in the cardiology ward. Table 3 showed that patients in the oncology ward had higher tendency to have psychotropic monotherapy as compared to patients in the cardiology ward (n=142, 88.8% versus n=134, 80.4%) (OR = 1.93, 95%CI: 1.03 – 3.59). Logistic regression analyses of psychotropic monotherapy showed that the odds of prescribing anxiolytics in the oncology ward were 4.6 times higher than antipsychotics (95%CI: 2.05 – 10.17). Proportion of patients having monotherapy with antipsychotics was the lowest among both cancer patients (6.3%) and patients with cardiovascular diseases (14.9%).

Table 3: The prescribing pattern of psychotropic drugs in oncology and cardiology wards.

	Oncology Ward N=160 n (%)	Cardiology Ward N=168 n (%)	OR* (95%CI)
Prescription pattern			
Monotherapy	142 (88.8)	135 (80.4)	1.93 (1.04 – 3.59)
Two or more psychotropic drug	18 (11.2)	33 (19.6)	1.00
Therapeutic group (Monotherapy)			
Anxiolytic, Hypnotics and Sedatives (N05B, N05C)	106 (66.3)	58 (34.5)	4.57 (2.05 – 10.17)
Antidepressants (N06A)	26 (16.3)	52 (31.0)	1.25 (0.52 – 2.99)
Antipsychotics (N05A)	10 (6.3)	25 (14.9)	1.00

*Logistic Regression analysis.

Among the prescriptions with psychotropic polypharmacy, the two most common concurrently used therapeutic groups were anxiolytics and antidepressants. Sixteen cancer patients (10%) and 15 patients in the cardiology ward were taking with these drugs concurrently.

Table 4: Utilization of psychotropic drugs in oncology and cardiology wards.

	Oncology Ward DDD per 100 bed-days	Cardiology Ward DDD per 100 bed-days	Ratio
Antidepressants (N06A)	33.43	47.80	1.43
Anxiolytic, Hypnotics and Sedatives (N05B, N05C)	25.65	26.34	1.03
Antipsychotics (N05A)	3.48	18.39	5.28
Total	62.56	92.53	1.48

DDD: defined daily dose.

Ratio: utilization in cardiology ward divided by utilization in oncology ward.

The sum of DDD per 100 bed days of psychotropic drugs was 62.56 in the oncology ward (Table 4). This figure indicated that about 63% (62.56/100) of occupants in the ward on average

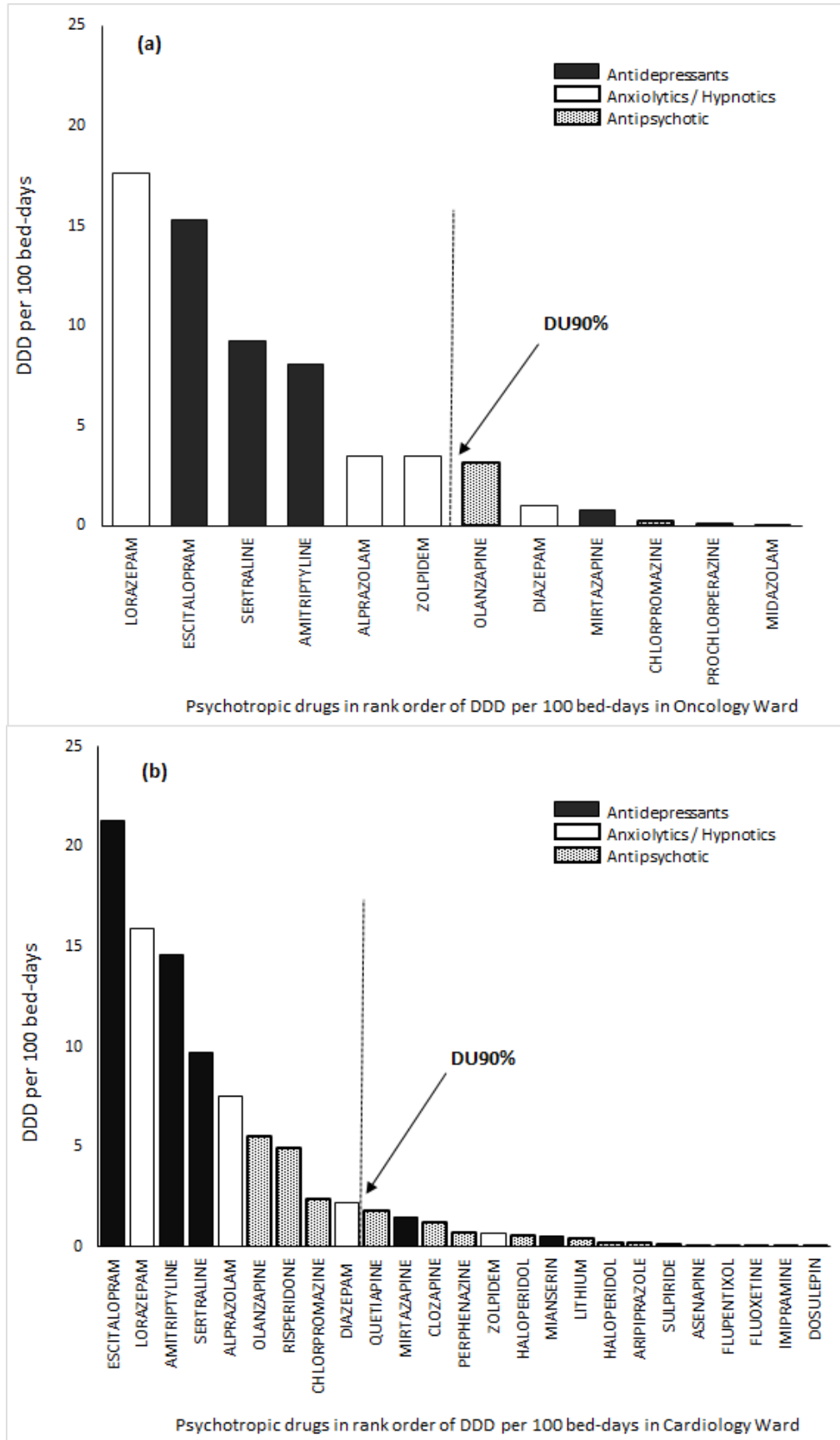


Fig. 1 (a) and (b): The drugs ranked by DDD per 100 bed-days in oncology ward and cardiology ward respectively. The vertical broken line and arrow indicate the drugs accounting for 90% of the total DDD per 100 bed-days in the respective wards.

might get a certain psychotropic drugs every day in the year. There was 1.5-fold variation (92.53/62.56) the total DDD per 100 bed days between oncology and cardiology wards. Utilization of antidepressants was the highest followed by anxiolytics and antipsychotics in both wards (Table 4).

Figure 1(a) and 1(b) presented the drug utilization of psychotropic drugs in rank order in oncology and cardiology wards respectively. A combination of six psychotropic drugs which comprised of 3 types of antidepressants and 3 types of anxiolytics, build the DU90% segment in the oncology ward. Lorazepam (17.7 DDD per 100 per days) was the highest utilized psychotropic drug in the oncology ward whereas escitalopram (21.3 DDD per 100 bed days) was highest in cardiology ward.

DISCUSSION

There were very few studies looking into the psychotropic prescription rate in cancer and cardiology patients. This is the first study comparing the utilization of psychotropic drugs in both groups of patients based on the calculation of daily defined dosage. Our results showed that the total usage of psychotropic drugs in cardiology was 1.5-fold of that in oncology ward. This current study also showed that approximately one in ten patients suffering from cancer were prescribed with an antidepressant, anxiolytic or antipsychotic in line with a systematic review (Walker *et al.*, 2013). Cancer patients had more than twofold odds of being prescribed with a psychotropic drug than patients with cardiovascular diseases. The most frequently prescribed therapeutic group of psychotropic drugs in the oncology ward was anxiolytics and this reflects similar finding from prior research (Ng *et al.*, 2014). Within the anxiolytic therapeutic group, the total defined daily dose of lorazepam was the highest followed by alprazolam in oncology and cardiology wards. Physicians generally prefer to prescribe lorazepam because of its antianxiety effect and its additional antiemetic properties (Jordan *et al.* 2007). On the contrary, alprazolam was less preferred probably because physicians wanted to avoid the risk of tolerance and drug dependence. However, our observations were inconsistent with the practice in Japan where alprazolam is the drug of choice for cancer patients suffering from major depression (Shimizu *et al.*, 2011). In Japan, the choice of anxiolytics was based on patient's life expectancy and their liver function (Okamura *et al.*, 2008). Alprazolam was prescribed as the first-line therapy to cancer patients with short life expectancy without hepatic impairment otherwise they will be prescribed with lorazepam (Shimizu *et al.*, 2011; Okamura *et al.*, 2008). Currently there is no specific guideline in the prescription of anxiolytic for cancer patients in Malaysia. Utilizing ATC/DD systems, it was interesting to find that the DDD per 100 bed days of psychotropic drugs in oncology ward was comparable to that of cardiology ward despite having populations of different socio-demographic and clinical background. Given to relatively larger proportion of cancer patients prescribed with anxiolytics, the DDD per 100 bed days indicates that patients in the oncology ward were prescribed with a

much lower dosage on average than patients in the cardiology ward. These observations may indicate that patients in oncology ward were taking lower dose of anxiolytics and had longer length of stay in hospital as compared to patients in the cardiology ward.

The DU90% method revealed that lorazepam was the highest utilized anxiolytics in terms of DDD per 100 bed days among cancer patients. However, when they were analyzed as a whole therapeutic group, the utilization of anxiolytics (25.65 DDD per 100 bed days) was lower than antidepressants (33.43 DDD per 100 bed days) (Table 3). Although the number of prescriptions for antidepressants was smaller than anxiolytics, this observation could be due to that antidepressants were prescribed at higher dose or for a longer duration. This finding suggests that larger number of prescriptions of psychotropic drugs does not indicate higher total defined daily dose. Drug utilization, represented by total defined daily dose, is determined by the dose prescribed and the duration it was prescribed for. Combining the total defined daily dose of antidepressants with ATC code N06AB revealed that selective serotonin reuptake inhibitors (SSRI) were the most utilized type of antidepressant in both oncology and cardiology wards. These findings are consistent with studies which shown that SSRI was the main drug of choice for treating anxiety and depression in cancer patients and patients with cardiovascular diseases (Elderson and Whooley, 2013). Evidence supports the use SSRI over other antidepressants among cancer patients because of its additional benefit in reducing hot flushes experienced by breast cancer patients particularly those who are taking tamoxifen therapy (Li *et al.*, 2011). Among patients with coronary heart disease and depression, a review published in 2011 showed a small beneficial effect of SSRIs on depression outcomes but no beneficial effects on mortality (Baumeister *et al.*, 2011). However, findings from a review by Rutledge and colleagues in 2013 showed reduction in cardiovascular diseases death and events through use of antidepressants in patients with coronary heart disease with co-morbid depression (Rutledge *et al.*, 2013). The latter study were able to show beneficial effect of antidepressants on mortality partly because the authors reviews articles from 1996 onwards – the beginning of the era of large psychological distress trials in cardiac patients with depression – to 2011, whereas Baumeister *et al.* reviewed trials from 1986 to 2009. This current study, in showing high utilization of SSRI may be attributed to its properties as weak inhibitors of cytochrome P-450 (CYP450) enzyme. Physicians and psychiatrists were presented with limited choice of antidepressants to prescribe because many anticancer drugs and cardiovascular drugs are metabolized by the CYP450 enzyme (Davies *et al.*, 2004). The three most commonly used antidepressants in our study (escitalopram, sertraline and amitriptyline) are known to be weak CYP450 enzyme inhibitors as compared to potent inhibitors such as fluoxetine (Davies *et al.*, 2004) making them the preferred drug of choice. Apart from the benefit of being a weak inhibitor of CYP450 enzyme, escitalopram (N06AB10) was also proven to be more effective than citalopram and had better tolerability than duloxetine in the treatment of major depression (Cipriani *et al.*, 2009). These are the possible

explanations for our findings that escitalopram emerged as the highest utilized antidepressant in the oncology and cardiology wards. The utilization of SSRIs was closely followed by tricyclic antidepressants which is similar to a study in Australia where 47% of cancer patients commenced therapy with SSRIs while another 33% of them with tricyclic antidepressant (Pearson *et al.*, 2015). Relatively high usage of amitriptyline, a tricyclic antidepressant, in cardiology ward observed in our study is of major concern because concomitant use of amitriptyline with beta-blockers was known to increase the risk of ventricular arrhythmias and hypotensive effects (Guaiana *et al.*, 2007). Physicians and psychiatrists should be reminded to avoid prescribing tricyclic antidepressants as the first-line therapy to treat major depression in patients with cardiovascular diseases (Elderson and Whooley, 2013). Our study highlights the importance to conduct drug utilization surveillance on a timely basis to improve the quality use of medicine. This study showed less than 10% of cancer patients were prescribed with monotherapy of antipsychotics. It was not surprising the antipsychotics contributed minimally to the overall psychotropic drug utilization in both oncology and cardiology ward. However, olanzapine may have been underutilized during the study period despite studies showing that low dose of olanzapine was effective in the treatment of chronic nausea (Jordan *et al.*, 2007) and improve symptoms of delirium among hospitalized cancer patients (Breitbart *et al.*, 2002). Gender, mean age and ethnicity of patients were significantly different between oncology and cardiology wards. Our finding on gender-differences among cancer patients was consistent with a previous study conducted at UMMC which reported 74% of cancer patients with anxiety with or without depression were female (Chan *et al.*, 2015). This observation was also in line with National Health Morbidity Survey in 2011 which reported the prevalence of females with depression were twice the rates of males (Institute for Public Health, 2011). High prevalence of female patients suffering from anxiety or depression was associated with the high prevalence of breast cancer (Chan *et al.*, 2015). However, our study could not relate the utilization rate of psychotropic drugs to a specific type of cancer as diagnosis was not examined in this study. Cancer patients in our study population were mainly Chinese (70.6%) which could be attributed to the location and catchment area of study center. Health seeking behavior may have an important role because, by ethnicity, Chinese were reported to be the highest proportion of people who utilized private healthcare facilities in Malaysia (Amal *et al.*, 2006). However, patients in cardiology ward prescribed with psychotropic drugs were mainly Indians probably because Indians had the highest prevalence of hypercholesterolemia and diabetes mellitus in Malaysia (Institute for Public Health, 2011). These conditions are risk factors leading cardiovascular diseases and explained the high percentage of Indians in the cardiology ward.

The strength of this study was the availability of electronic pharmacy database that ensures the completeness prescription records at patient level. Using the ATC/DDD system provide minimal misclassification of psychotropic drugs to their therapeutic groups and create an opportunity for a valid

international comparison (World Health Organization, 2014). Drug utilization was measured as DDD per 100 bed days enabled them to be used as a reference or baseline for future studies. These units of measurement were deemed appropriate by the WHO when comparing drug consumption between multiple wards (World Health Organization, 2014). The risk of bias is minimal in this study because all patients who were admitted into oncology and cardiology wards were recruited. Since we did not collect any information from medical records, results from this study must be interpreted with caution. The absence these information inhibits the measurement of confounding factors such as duration of psychological distress, indications for psychotropic drugs prescriptions, type of cardiovascular diseases and cancer-related factors such as disease progression. It is also important to note that not all psychotropic drugs are available in UMMC pharmacy due to formulary restrictions; the drug utilization pattern may have been subjected to the availability of psychotropic drugs. Nevertheless, we suggest future studies in this research area to be conducted prospectively where patients with existing psychiatric condition should be excluded at the initial of study. The study should follow-up patients who are free of psychiatric diseases from first day of admission, observe if any psychological distress occur and record the psychotropic drugs prescribed.

CONCLUSION

In conclusion, this study highlights some key issues on psychotropic drug utilization. First, the calculated total dosage of psychotropic drugs utilized can be employed as a reliable guidance as the burden of psychological distress in patients with any medical conditions other than cancer or heart diseases. Antidepressant was the most utilized pharmacological intervention for psychological distress in both oncology and cardiology wards, followed by anxiolytic, hypnotics and sedatives while antipsychotics were the least utilized. Secondly, given the high percentage of patients in oncology ward being prescribed with psychotropic drugs and importance of early initiation of treatment, screening for psychological distress among hospitalized cancer patients is recommended.

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