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Original article

Anticholinergic burden risk and prevalence of medications carrying anticholinergic properties in elderly cancer patients in Jordan

Ahmad Al-Azayzih [a,*], Anan S. Jarab [a,b], Enas Bani-Ahmad [a], Saja Smadi [a], Zelal Kharaba [b,c], Khalid A. Al-Kubaisi [d]

[a] Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology. P.O. Box 3030, Irbid 22110, Jordan
[b] College of Pharmacy, AL Ain University, Abu Dhabi, United Arab Emirates
[c] Honorary Associate Lecturer, Faculty of Medical Sciences, Newcastle University, Newcastle upon tyne, UK
[d] Department of Pharmacy Practice and Pharmacotherapeutics, College of Pharmacy, University of Sharjah, Sharjah, United Arab Emirates

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ABSTRACT

Background: Geriatric cancer patients are susceptible to adverse drug events due to the complexity of their chemotherapy regimens and collateral treatments for their comorbid conditions. Prescribing medications with anticholinergic burden characteristics can complicate their condition, leading to negative impacts on their health outcomes and quality of life, including an increase in adverse drug event frequency, physical and cognitive impairments.

Objective: This study aims to examine the prevalence of anticholinergic prescribing and identify the cumulative anticholinergic load risk associated with drugs prescribed to elderly cancer patients. Also, to identify the predictors that might lead to raised anticholinergic burden in these patients.

Methodology: This retrospective cross-sectional study included elderly patients (age $\geq$ 65) diagnosed with cancer and admitted to the adult oncology unit at King Abdullah University Hospital (KAUH) in Jordan during the period between (January 1st, 2019, and January 1st, 2022). The medication charts of 420 patients were evaluated for study outcomes.

Results: Of the total subjects, females represented 49.3%, and the average age was 72.95 (SD = 7.33). A total of 354 (84.3%) patients were prescribed at least one drug carrying anticholinergic burden properties. Median for anticholinergic medications was 3 (IQR = 4). Our study found that 194 (46.2%) patients were at a high risk of adverse events associated with anticholinergic load (cumulative score $\geq$ 3). Metoclopramide, furosemide, and tramadol were the most frequently prescribed drugs with anticholinergic properties. Alimentary tract drugs with anticholinergic action were the most commonly encountered items in our study population.

Conclusion: Our study revealed a significantly high prevalence of anticholinergic prescribing among elderly cancer patients. Nearly half of the patients were at high risk of developing serious effects related to anticholinergic activity from the drugs administered. Polypharmacy was strongly associated with increased anticholinergic burden score. Evidence-based recommendations utilizing prescribing strategies for safer alternatives and deprescribing of inappropriate medications could reduce such inappropriate prescribing.

1. Introduction

Anticholinergic drugs are commonly prescribed among patients worldwide, despite their potential side effects. These side effects range from classical manifestations such as dry mouth, blurred vision, and constipation to more advanced adverse effects such as confusion, delirium, cognitive impairment, dementia, and increased falls and mortality risk (Tune, 2001). Elderly patients are at high risk of developing drug-related adverse effects due to the fact that with aging, more chronic conditions develop,

* Corresponding author.
E-mail address: aaazayzih@just.edu.jo (A. Al-Azayzih).

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necessitating the administration of more medications to control these problems (polypharmacy) and stabilize their disease condition (Canio, 2022; Choi et al., 2023).

Anticholinergic side effects incidence and severity are generally augmented by administering more than one drug with anticholinergic effects at the same time, which can be a problem for elderly patients who are often on multiple medications (Salahudeen et al., 2015b; Tristancho-Perez et al., 2021; Villalba-Moreno et al., 2018) elderly patients are more prone to anticholinergic adverse events, especially those affecting the central nervous system, owing to an elevated blood–brain barrier permeability of these medications (Campbell et al., 2009; Chancellor et al., 2012). These side effects impact geriatrics more than other age groups because of aging-associated shortage in cholinergic signaling centrally (Sultzer et al., 2022).

In addition, the changes in both pharmacokinetics and pharmacodynamic parameters encountered in elderly patients will expose them to more chances of side effects, especially life-threatening adverse events (Mangoni & Jackson, 2004; Sumpio et al., 2016; West et al., 2013).

Management of cancer and terminally ill patients is generally complex and time-consuming. Treatment of patients with cancer depends mainly on various treatment modalities, including chemotherapy protocols, where the use of different anticancer drugs with different mechanisms and adverse effects profiles is compulsory (Sumpio et al., 2016).

The current number of elderly patients living with cancer in Jordan is increasing due to increased life expectancy among the population over the past years (Al-Azayzih et al., 2020), and in addition to a noticed increase in the prevalence of various tumors in the same group (Abdel-Razeq et al, 2022; Abdel-Razeq et al., 2020). In addition to cancer, geriatric patients often have other types of chronic conditions and comorbidities, such as cardiovascular, psychological, neurological, diabetes, and other health problems, making the treatment scenario in these patients highly complicated (Williams et al., 2016).

1.1. Research aim

Evaluating the anticholinergic burden and inappropriate prescribing behavior among the elderly population is a priority. Therefore, the aim of our research is to assess the prevalence of anticholinergic prescribing, cumulative anticholinergic burden of medication utilized, and to identify the major predictors associated with anticholinergic prescribing in geriatric population surviving cancer. This study should provide a basis for future prescribing recommendations to eliminate the serious side effects that might result from taking medications with anticholinergic characteristics.

2. Methodology

2.1. Study design and Setting

This retrospective cross-sectional study was conducted on elderly patients (Age in years $\geq$ 65) who were diagnosed with either solid or hematological cancers and admitted to the adult oncology department at King Abdullah University Hospital (KAUH) during the period between January 1st, 2019, and January 1st, 2022), KAUH is considered as the main referral center for cancer patients in the North of Jordan.

2.2. Sample size Calculations

Sample size was calculated according to Krejcie and Morgan formula (Krejcie and Morgan, 1970) to obtain 50% population proportion (to achieve the highest number of subjects) and a 95% confidence interval with a margin of error of 5%. A total number of 384 subjects or more were required to meet the sample size calculation of the predetermined parameters values.

2.3. Patients characteristics and data Collection

A total of 420 patients were included in the study, electronic medical and clinical charts from the KAUH electronic medical system for specific patients were assessed retrospectively for further data extraction and analysis. Patients' characteristics such as gender, average age, and frequency of specific cancer were collected. The frequency of drugs with anticholinergic potency was evaluated and calculated based on the list reported by CRIDECO Anticholinergic Load Scale (CALS) score (Ramos et al., 2022). CALS was developed by group of researchers from Spain after running an intensive systematic review and comparing list of anticholinergic drugs included in the previous seven scores including Anticholinergic drug scale (Carnahan et al., 2006), Anticholinergic Risk Scale (Rudolph et al., 2008), Anticholinergic Cognitive Burden Scale (Campbell et al., 2009), Duran Scale (Duran et al., 2013), Salahudeen Scale (Salahudeen et al., 2015a), German Anticholinergic Scales (Kiesel et al., 2018), and Korean Anticholinergic Activity Scale (Jun et al., 2019). CALS list includes a total of 217 drugs with anticholinergic effects, which were further classified into three categories based on their anticholinergic potency: drugs with low anticholinergic potency (score = 1) and total of 125 medications in this category, drugs with medium anticholinergic potency (score = 2) with 28 drugs in medium potency category, and drugs with high anticholinergic potency (score = 3) with 62 drugs in the high potency category. The drugs with anticholinergic properties administered to patients were also categorized according to the Anatomical Therapeutic Chemical (ATC) system (WHO). The ATC data were represented as the frequency of the total number of drugs belonging to each individualized ATC category. Finally, the cumulative anticholinergic burden was counted for each patient utilizing the updated CALS score. Briefly, the burden score for each drug taken by each patient was added together to obtain the final cumulative anticholinergic score (0, 1, 2, 3, 4, or $\geq$ 5). A cumulative score of 3 or more was considered a high burden score.

2.4. Statistical analysis

The data was entered and analyzed using Microsoft 365 Excel. Descriptive statistics were performed to describe the elderly cancer patients' characteristics. Both continuous and categorical parameters were presented as a sum, average ± standard deviation, median (IQR) and frequency, respectively. Multivariable logistic regression module was applied to examine potential predictors associated with anticholinergic risk burden increase. Statistically significant difference was assumed at P value of less than 0.05.

3. Results

The results of the study indicate that a total of 420 geriatric cancer patients were analyzed, with 207 (49.3%) being female. The average age of the study sample was 72.95 (SD = 7.33) years. Median of total medications prescribed was 10 (IQR = 7), while median for anticholinergic medications was 3 (IQR = 4). Polypharmacy index of $\geq$ 5 drugs was present in 362 patients (86.2%). Breast cancer (16.2%), colorectal (13.1%), and lung cancer (12.86%) were found to be the most common cancers among the study population (Table 1).

The study found that a total of 33 medications with anticholinergic effects were administered to patients. Metoclopramide was

Table 1
Patients Characteristics.

Variable	Category	N ± SD Or Median (IQR)	Percentage (%)
Gender	Male	213	50.7%
	Female	207	49.3%
	Both	420	100%
Average Age (years)		72.95 (SD = 7.33)	
Median (IQR) of Total Medications Prescribed		10 (7)	
Median (IQR) of Anticholinergic Medications Prescribed		3 (4)	
Patients who have Polypharmacy (≥5 Prescribed Medications)		362	86.2%
Types of solid and hematological cancers	Brest Cancer	68	16.20%
	Colorectal	55	13.10%
	Lung	54	12.86%
	Bladder	40	9.52%
	Prostate	25	5.60%
	stomach	22	5.23%
	Endometrial	19	4.50%
	Lymphoma	18	4.28%
	Leukemia	17	4.07%
	Multiple Myeloma	13	3.10%
	Pancreatic	13	3.10%
	Ovary	12	2.86%
	Liver	12	2.86%
	Kidney	10	2.38%
	*Others	42	10%

* Others: (include, esophageal, brain, gall gladder, skin, bone and connective tissue, peritoneal mesothelioma, parotid gland, adrenal gland, thyroid, thymus, submandibular gland, urethra, tongue, nasopharynx, ... etc.).

Table 2
Most common anticholinergic agents prescribed for patients.

Drug	Total Anticholinergic Drug Users N = 354 (% of total N)	Anticholinergic Potency (Scale 1–3)
Metoclopramide	150 (42.4%)	1
Furosemide	129 (36.4%)	1
Tramadol	85 (24.0%)	2
Bisacodyl	60 (16.9%)	1
Metoprolol	55 (15.5%)	1
Chlorpheniramine	53 (15.0%)	3
Metformin	50 (14.1%)	1
Hydrocortisone	50 (14.1%)	1
Alprazolam	41 (11.6%)	1
Loperamide	37 (10.5%)	1
Ranitidine	31 (8.8%)	2
*Codeine	29 (8.2%)	1
Fentanyl	29 (8.2%)	1
Prednisolone	25 (7.1%)	1
Olanzapine	15 (4.2%)	2
Vancomycin	13 (3.7%)	1
*Pseudoephedrine	11 (3.1%)	1
Warfarin	10 (2.8%)	1
Nifedipine	9 (2.5%)	1
Mirtazapine	8 (2.3%)	1
*Orphenadrine	7 (2.0%)	3
Domperidone	7 (2.0%)	1
Hyoscyamine or Hyoscine	7 (2.0%)	3
Quetiapine	6 (1.7%)	2
Carbamazepine	6 (1.7%)	2
Valproic Acid	4 (1.1%)	1
Amitriptyline	4 (1.1%)	3
Gentamycin/ Gentamicin	4 (1.1%)	1
Citalopram	4 (1.1%)	1
Escitalopram	3 (0.8%)	1
Theophylline	2 (0.6%)	1
Famotidine	2 (0.6%)	1
Amantadine	1 (0.3%)	2

*Codeine was in combination with Paracetamol (Paracetamol 500 mg + Codeine Phosphate 10 mg) Tablet.
*Orphenadrine was in combination with Paracetamol (Orphenadrine 35 mg + Paracetamol 450 mg) Tablet.
*Pseudoephedrine was in cough mixture (Guaifenesin 100 mg + Pseudoephedrine 20 mg).

the most frequently administered medication with anticholinergic properties, with a frequency (n) of 150 (42.4%), followed by furosemide (n = 129 (36.4%)), and tramadol (n = 85 (24.0%)) (Table 2). Furthermore, results indicated that percent of patients with at least 1 anticholinergic was 84.3%, Also, the pie chart (Fig. 1) showed that patient's number, n (%) who were taking specific number of anticholinergic medications (1,2,3,4, and ≥ 5) were as follow: 109 (30.8%), 80 (22.6%), 72 (20.4%), 49 (13.8%), and 44 (12.4%); respectively. Additionally, in terms of medication categories, alimentary tract medicines (Frequency = 340) were the most frequently administered anticholinergic medicines, followed by drugs that work on the nervous system (Frequency = 235), cardiovascular system (Frequency = 203), respiratory tract and antiallergic medicines (Frequency = 141), anti-infective medicines for systemic use (Frequency = 17), and musculoskeletal system (Frequency = 7) (Fig. 2).

The study also aimed to determine the cumulative anticholinergic burden score in patients. The results revealed that 354 (84.3%) patients were prescribed at least one anticholinergic medication, with 97 patients having a cumulative score of 1, 60 patients having a score of 2, 57 patients having a score of 3, 36 patients having a score of 4, and 104 patients having a cumulative score of 5 or more. The highest cumulative score reported among patients was 13 (Table 3).

Investigating the possible variables which might be associated with increased the anticholinergic burden among older cancer patients. This study evaluated polypharmacy, age, gender, and type of cancer as predictive variables for anticholinergic burden score increment. Only polypharmacy was associated significantly with more odds of higher anticholinergic burden score (Table 4).

Overall, these findings suggest that a substantial proportion of geriatric cancer patients were prescribed medications with anticholinergic properties, which can potentially lead to an increased risk of adverse events. The identification and monitoring of anticholinergic burden in this vulnerable population may help to optimize their medication regimens and improve their overall quality of life.

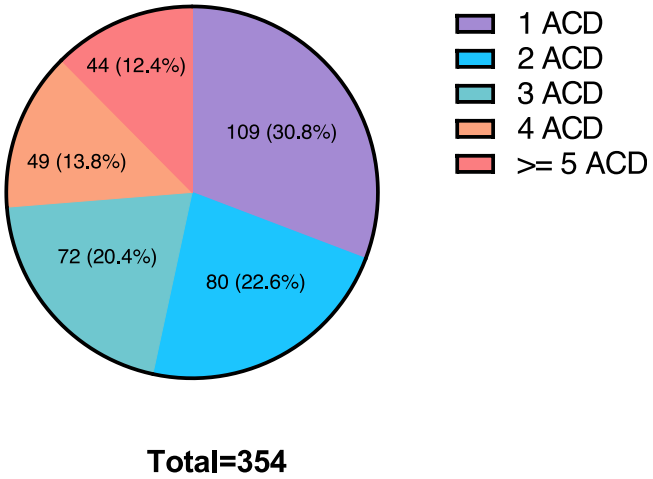

Fig. 1. % Patients with at least 1 anticholinergic medications = (354/420) = 84.3%. Number in the pie chart represent number of patients (%) with specific number of anticholinergic drugs (ACD).

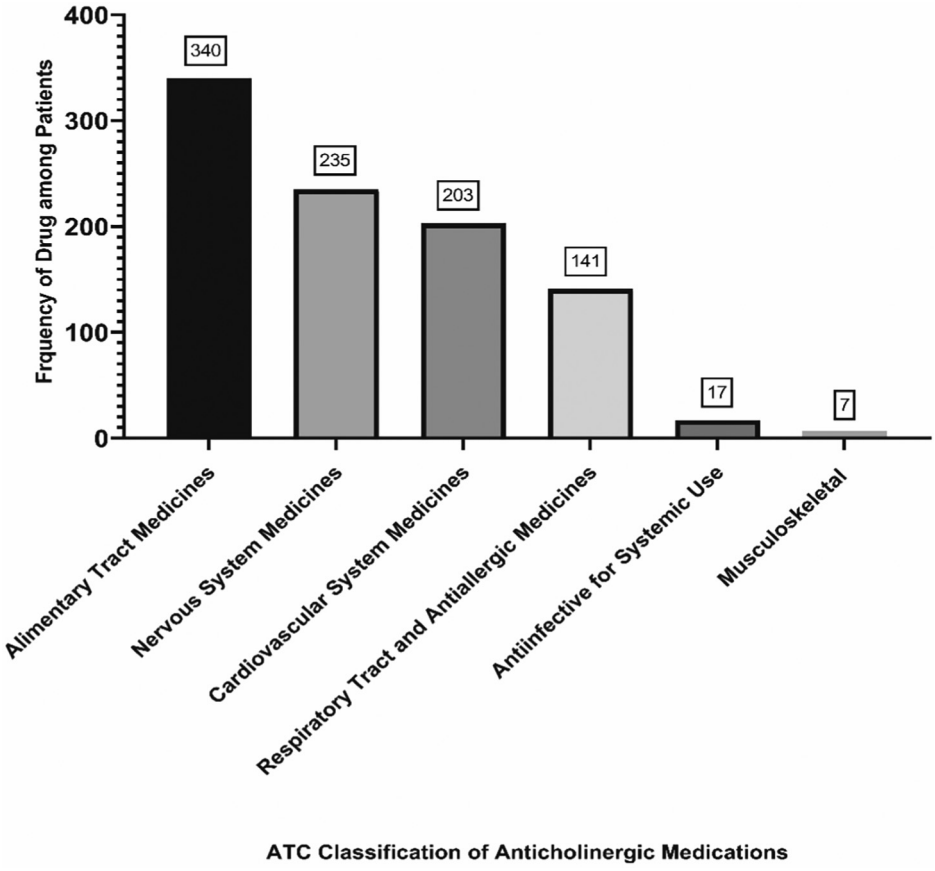

Fig. 2. Classification of Anticholinergics Medications According to Anatomical Therapeutic Chemical (ATC) Classification System.

Table 3
Anticholinergic Burden Score for Patients (N = 420).

Cumulative Anticholinergic Burden Score	Number of Patients with Anticholinergic Score
0	66
1	97
2	60
3	57
4	36
≥5	104
Total	420

Table 4
Multivariable logistic regression: dependent variable is anticholinergic drugs burden score.

Variable	OR (95%CI)	P-value
Polypharmacy	1.532 (1.378–1.703)	*<0.001
Age	1.008 (0.963–1.054)	0.740
Gender (Male)	1.731 (0.899–3.333)	0.101
#Type of cancer	1.267 (0.462–3.475)	0.646

* P < 0.05 was considered statistically significant.
# Solid or Hematological Cancers.

4. Discussion

This study is the first to evaluate the prevalence and prescribing attitude, as well as identifying the cumulative anticholinergic burden of medications with anticholinergic effects among elderly cancer patients in Jordan.

Results of this study showed that 84.3% (n = 354 out of 420) of the study patients had been exposed to at least one anticholinergic drug with different anticholinergic potency. Surprisingly, our data found that around one-quarter of the patients had a cumulative burden of ≥5 (n = 104 out of 420) where the highest cumulative score reported equal to 13. Compared to previous reports, our results indicated an elevated prescribing and administration of drugs with anticholinergic burden in our study subjects. Recent studies from all around the world showed significant variations in prevalence rates of anticholinergic effects exposure. (Cebron Lipovec et al., 2020; Cross et al., 2016; Havnes et al., 2023; Mantri et al., 2019; Mayer et al., 2017; Salahudeen et al., 2015b; Tristancho-Perez et al., 2021). This significant difference in our study regarding anticholinergic burden prevalence could be due to many factors, including first, the utilization of a newer anticholinergic burden scale (CALS) where the list of potential anticholinergic drugs contains 217 drugs (Ramos et al., 2022). In contrary to other scales where the list of drugs has between (49–195) medications (Carnahan et al., 2006; Duran et al., 2013; Rudolph et al., 2008; Salahudeen et al., 2015a). Also, polypharmacy and the complex nature of treatment modalities in elderly cancer patients might signify the opportunities for these drugs prescribing (Canio, 2022; Sumpio et al., 2016).

Different drugs were identified to carry anticholinergic burden and were taken by our study patients. Metoclopramide was at the top of the list, followed by furosemide and tramadol. While it is common to see metoclopramide prescribed for cancer patients to control their breakthrough nausea and vomiting, it is still recommended to minimize the exposure of metoclopramide by prescribing appropriate pre-chemotherapy medications for nausea and vomiting (Davis et al., 2021). On the other hand, opioid

analgesics (tramadol) and other psychotropic medications such as alprazolam, olanzapine, quetiapine, mirtazapine, valproic acid, amitriptyline, and citalopram and escitalopram were commonly prescribed in this study with high agreement to previous reports outcomes indicated that opioids analgesics and other psychotropic drugs are highly prevalent and represent a major source of anticholinergic burden in both geriatrics and cancer populations (Cebron Lipovec et al., 2020; Gorup et al., 2018; Lopez-Alvarez et al., 2019).

Interestingly, alimentary tract medicines according to ATC classification followed by drugs that work on the central nervous system and cardiovascular system were the most common medicines prescribed among study subjects. For example, ranitidine was frequent in 31 patients carrying an anticholinergic potency score equal to 2. According to a randomized clinical trial, proton pump inhibitors are considered much safer medications to replace ranitidine prescribing, knowing that PPI carries no known anticholinergic burden effects when used either chronically or as needed by elderly patients (Hansen et al., 2006). Chlorpheniramine, a first-generation antihistamine with a definite anticholinergic burden (score = 3), was encountered in 53 patients, representing 14.9% of the total number of patients. While it is highly discouraged to use first-generation antihistamines in the senior population, second-generation antihistamines such as loratadine and fexofenadine (anticholinergic potency score = 1) provide a better and safer alternative to these patients, carrying minimal anticholinergic activity compared to chlorpheniramine (Ramos et al., 2022).

According to several studies, a cumulative anticholinergic burden $\geq$3 will render the patients at high risk of falls, cognitive impairments, delirium, and dementia (Lisibach et al., 2021). Unfortunately, our study revealed that around 25% of the patients scored a cumulative burden risk of 5 or more. Polypharmacy was reported in several studies to be associated with rise in the cumulative anticholinergic burden, thus, growing risk of falls and cognitive impairment among elderly patients. (Bourrel et al., 2020; Okudur et al., 2021). Our results were in agreement with those reports suggesting a greater correlation between polypharmacy and higher cumulative anticholinergic burden and risk of falls and other adverse events in elderly compared to age and comorbidities (Wong et al., 2023).

4.1. Study limitations

This study was conducted retrospectively with cross-sectional design. Hence, can't address the cause and effects associations. Also, due to the retrospective design, data were extracted from the electronic medical charts of the patients, thus, reporting actual adverse events related to anticholinergic drugs action was not feasible. The study was conducted utilizing patients from only one cancer hospital (KAUH) in Jordan. Therefore, the extrapolation of the study findings might be affected to little extent, due to different reasons, first, the KAUH does serve large and highly populated geographical area in Jordan. Second, KAUH is one of the major hospitals in Jordan which specialized in treating different types of solid and hematological diseases.

5. Conclusion

The prevalence of drugs carrying anticholinergic burden risk was high among elderly cancer patients. The most commonly prescribed medications associated with anticholinergic risk were drugs that work on the alimentary tract, followed by those that affect the central nervous system and cardiovascular system. The cumulative anticholinergic burden, which is associated with a risk of serious adverse events, was found to exist in almost half of the patients and polypharmacy was the mainly predictor for cumulative anticholinergic burden increment. There is no doubt that there is a crucial need to adopt preventative prescribing and prescribing measures to minimize the risks associated with the use of drugs with anticholinergic burden in geriatric cancer patients.

Ethical approval

Institutional ethical approvals were obtained as per institutional research board (IRB) requirements at KAUH (King Abullah University Hospital), IRB Approval number (KA 61/147/2022). Data confidentiality was ensured by the authors throughout the whole process of study period and under the responsibility of the corresponding author according to IRB regulations. Patients' identification numbers were replaced by serial numerical numbers.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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