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Original article

Polypharmacy and drug interactions amongst cirrhotic patients discharged from a tertiary center: Results from a national quality improvement audit

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ABSTRACT

Background and Study Aims: Auditing of polypharmacy is particularly essential in patients with cirrhosis because of the crucial role of liver in drug metabolism. The aim of this study was to audit the drug prescribed in this group of patients and analyzed the quantity and severity of potential drug-drug interaction.

Patients and Methods: In this cross-sectional study we analyzed the last prescription as recorded in the Electronic Medical Record at the time of discharge for cirrhotic patients who were hospitalized during 24-months study period. Data were also collected for age, gender, and diagnoses. The drugs were analyzed for cross interactions using the Lexicomp-online e-formulary. The drug interactions are classified as: class A: no known interaction, class B: no action needed, Class C: monitor therapy, class D: consider therapy modification, and Class X: the drug should be avoided.

Results: A total of 333 patients with cirrhosis were audited, whereas complete and relevant data were available for 181 patients (134 males, 74%) with a mean age ± SD 59.7 ± 10.1. Out of these, 168 (92.8%) patients were using at least one medicine and the total number of medications used was 808 drugs. The observed average of utilization was 7.8 ± 3.1 drugs (range = 1–17) and 102 (56.3%) patients used polypharmacy. A total of 198 (24.5%) consumed drugs were related to cirrhosis and its complications. Six (3.3%), 30 (16.6%) and 65 (35.9%) patients had Class-X, Class D, and Class C, respectively. Utilization of polypharmacy was statistical significant in patients with class X (83.3%, p = 0.03), class D (16.6%, p = 0.01), and class C (35.9%, p = 0.02).

Conclusion: The findings highlight the importance of auditing for polypharmacy to recognize and prevent potential drug-related problems in patients with cirrhosis. Implementation of strategies to optimize medication use in patients with cirrhosis should be considered necessary as it can have a bearing on length of stay and morbidity.

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Introduction

With increasing life expectancy, there has been a commiserate increase in co-morbidities (associated with ageing), and the pharmacotherapy that inevitably accompanies it [1,2]. Polypharmacy in its basic form refers to intake of multiple medications both for primary and associated comorbidities. The exact number of medications that constitutes polypharmacy however has continue to remain the subject of unresolved therapeutic debate [3,4]. A recent systematic review of (N = 138) definitions of polypharmacy reported intake of ≥5 medications as the most commonly reported definition of polypharmacy (n = 51, 46.4%) [5]. Added to this uncertainty is the clinically consequential variability of definitions depending on the clinical settings [5]. Polypharmacy could both be appropriate (where each medication is matched by a clinical need), and inappropriate (where there's lack of clear therapeutic objective or rigor in the indication for the prescribed drugs) [6]. Unfortunately, polypharmacy is not without morbidity and

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sometimes unacceptable mortality [7]. Increase in the number of prescriptions for example has been associated with an increase in risk of both drug-drug as well as drug-food interactions [8]. This risk is exponentially higher in patients with primary morbidities involving metabolizing organs such as cirrhotic patients and those with chronic kidney disease [8].

The uncertainty regarding the exact burden of polypharmacy remains unresolved both for the hospitalized cirrhotic patients and those who are about to be discharged from hospital after admission for multiple clinical problems. Cirrhotic patients are at increased risk for potential drug-drug interactions and have a multiplicative risk of adverse drug reactions (ADR) sometimes exponentially tied to the severity of their disease [9]. Understanding this burden especially in the cohort of patients leaving hospital, will be important for health care providers in devising, commissioning, and implementing strategies aimed at reducing the risk of ADR's which are sometimes associated with these admissions. In addition, this will also assist in reducing the rates of inappropriate prescribing, and the sequelae that come with it (including mortality). Auditing national databases have long been recognized as a veritable tool for reflecting on practice within defined settings (or clinical environment), as well identifying trends that could both serve as a signal for hypothesis generation, or service improvement models.

In this cross-sectional audit, we have for the first time described the phenotype of polypharmacy amongst cirrhotic patients about to be discharge from hospital, as well as explored the factors that contribute to or exacerbate the attendant ADR's associated with them. The aim of this study was to audit the drug prescribed in this group of patients and analyze the quantity and severity of potential drug-drug interaction.

Patients and methods

This cross-sectional study for adult cirrhotic patients was conducted at Weill Cornell Medicine-affiliated tertiary medical center in Doha Qatar (Hamad General Hospital) during the 24 months period (January 2018- December 2019). We analyzed the last prescription [in Electronic Medical Record (EMR)] at the time of patient's discharge from hospital. The patients included were those admitted to the medical wards for more than 24 h and discharged on at least one medication during the study period. Clinical and demographic data were collected for parameters including age, gender, and admission diagnoses, number and types of comorbidities, length of stay, and number and pharmacological class of the prescribed medications on discharge were collected. Patients admitted for surgical procedures were excluded. The diagnosis of cirrhosis was based on the combination of clinical, laboratory and imaging findings [10].

The drugs were analyzed for cross interactions using the Lexicomp-online e-formulary. The drug interactions are classified as class A: no known interaction, class B: no action needed, Class C: monitor therapy, class D: consider therapy modification, and Class X: the drug should be avoided.

Polypharmacy was defined as the simultaneous use of multiple drugs (≥5 drugs) by a single patient, for one or more conditions. Drug-drug interaction is defined as a change in a drug's effect on the body when the drug is taken together with a second drug.

Statistical analysis

Descriptive statistics were used to describe the data. For continuous variables, the mean and standard deviation (SD) were used to summarize the data. For categorical variables, frequencies and percentages were reported. The differences between groups were analyzed using Pearson's chi-squared test or Fisher's exact test. A *p*-value of <0.05 was considered statistically significant. The data were processed and analyzed using SPSS Statistics (SPSS Statistics Inc., Chicago, US, version 22).

Results

The total number of patients audited for this study was 333, out of which complete data were available for 181 patients. Table 1 shows their demographic and clinical characteristics. Out of these 181 patients, there were 134 (74%) males and 47 (26%) females with a mean age ± SD 59.7 ± 10.1. Fig. 1 shows the distribution of used medications among the study population. There were 168 (92.8%) patients who reported the use of at least one medicine. The audit found that the total number of medications used was 808 drugs. The observed average of utilization was 7.8 ± 3.1 drugs (range = 1 to 17), and 102 (56.3%) patients used polypharmacy with use ≥5 drugs. Only 198 (24.5%) consumed drugs were related to cirrhosis and its complications and the majority of drugs accounting for other pharmacological classes (Fig. 2). By analyzing the drugs for a cross drug-drug interaction, 6 (3.3%), 30 (16.6%) and 65 (35.9%) patients had Class-X, Class D, and Class C, respectively. Utilization of polypharmacy was statistical significant in patients with class X (83.3%, p = 0.03), class D (16.6%, p = 0.01), and class C (35.9%, p = 0.02.

Discussion

We found out that a significant proportion of patients with cirrhosis were on polypharmacy. Additionally, a significant percentage of the drugs constituting polypharmacy in our study were due to multi-morbidity of the patients and were not part of primary pharmacotherapy for their cirrhotic liver disease. The findings of the present audit are consistent with recent reports from other centers that have shown an increasing trend towards polypharmacy amongst patients with chronic liver disease from diverse etiologies especially non-alcoholic fatty liver disease [11]. Our study patient cohort was relatively older, which may have accounted for the high proportion of polypharmacy in our report. With increasing age, the proportion of multi-morbidity requiring varying pharmacotherapy also rises exponentially; a setting that promotes the development and perpetuation of polypharmacy.

Table 1
Demographic and clinical characteristics of cirrhotic patients

Characteristics	Number = 181
Age, mean ± SD, year	59.7 ± 10.1
Gender, male, n (%)	134 (74)
Number of medications, mean (range)	7.8 (1–17)
≥5 medications (%)	102 (56.3)
Number of comorbidities*, mean (range)	3 (1–5)
Comorbidity greater than 1 (%)	132 (72.9)
Etiology of cirrhosis	43 (23.8)
- Hepatitis B, n (%)	63 (34.8)
- Hepatitis C, n (%)	46 (25.4)
- Alcoholic, n (%)	19 (10.5)
- Other etiology**, n (%)	10 (5.5)
- Cryptogenic, n (%)	
Child-Pugh grading	88 (48.6)
- Grade A, n (%)	75 (41.4)
- Grade B, n (%)	18 (10)
- Grade C, n (%)	
Length of stay, mean (range), day	7 (3–13)

* Comorbiditis: diabetes mellitus, hypertension, cardiovascular disease, dyslipidemia, chronic kidney disease.
** Non-alcoholic fatty liver disease, primary biliary cholangitis, autoimmune hepatitis.

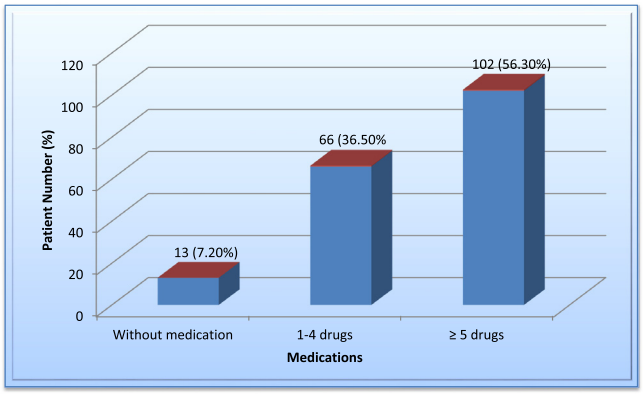

Fig. 1. Distribution of medications used by patients with cirrhosis.

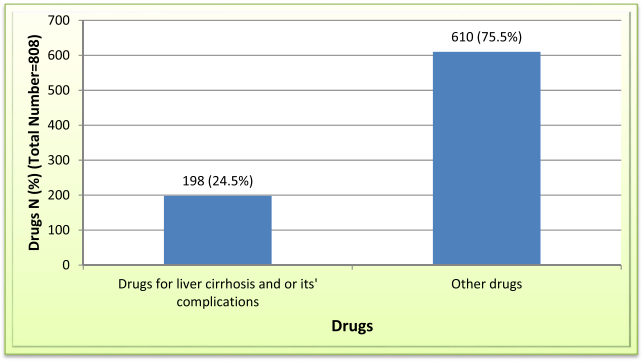

Fig. 2. Pharmacological classes of medications prescribed on discharge.

The annual rate of hospitalization for patients with cirrhosis worldwide has been estimated at around 3 per year [12]. Very often these patients are too unwell to have a reliable and dependable discussion of the list of their "usual" medications, creating a subsisting platform for both drug errors and unwarranted prescribing [13]. The median length of in-hospital stay for our patient cohort was 7 days (IQR 3, 13). Longer hospital stays have the potential to both enable robust discussion and adequate reconciliation of patient's medications (and therefore reduced risk of inappropriate prescribing); but also portends inherent risk of acquired in-hospital morbidities including healthcare-associated infections.

The predominant phenotype of classes of drug liable to potential interaction in our study population was favorable (classes A and B). In patients with liver cirrhosis especially in the setting of polypharmacy, drug classes C and D combination should be avoided, owing to additive risk of serious interaction. The net effect of the latter in this cohort of patients is of a magnitude higher than those in the general population. It is therefore of utmost therapeutic importance for good and monitored prescribing practices to be adhered to when dealing with these patients. Specific example of drug combinations that should be avoided in patients with liver cirrhosis includes combination of Opoids (such as codeine) with Benzodiazepines (especially Zolpidem); other combinations include strong opiates (such as Methadone) with antipsychotic agents amongst others.

There is, therefore, the need for more prospective work in both ascertaining the exact burden of polypharmacy amongst these cohorts of patients, their determinants, as well as the impact of remedial measures such as drug reconciliation (amongst other measures on inappropriate polypharmacy).

The strength of our study lies in its exploration of the growing burden of polypharmacy in this vulnerable population with hitherto limited data to support any therapeutic planning. Additionally, it is hypothesis-generating as it will assist in the design of future prospective studies that will possibly explore different themes of this ever-increasing morbidity.

In conclusion, the findings of this report highlight the potential of adverse morbidity associated with polypharmacy as well as the need for implementation of strategies to optimize medication use in patients with advanced liver disease.

Funding

Nil.

Ethical consideration

The department chairman approved this work as a quality project, and no formal IRB approval was sought as it was part of a quality improvement initiative.

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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