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Review article

Increasing Cancer Survival and The Emerging Economic Impact of Polypharmacy: A Therapeutic Perspective

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Abstract

Polypharmacy, the concurrent use of multiple medications, is common amongst cancer patients, and often leads to an increased economic burden. This burden is primarily driven by higher medication acquisition expenses and healthcare utilization costs. The direct costs associated with polypharmacy include the high expenses of cancer treatments, supportive medications, and drugs for managing comorbidities. Limited insurance coverage further exacerbates the economic burden, as patients often face substantial out-of-pocket expenses. Polypharmacy in cancer survivorship also results in increased healthcare utilization and associated costs due to adverse drug events, drug interactions, and treatment-related complications. These factors necessitate hospitalizations, emergency department visits, and outpatient care, all of which contribute to the economic impact. Moreover, managing long-term effects and chronic conditions resulting from cancer treatments and aging further adds to the economic burden of polypharmacy. The addition of multiple medications to manage these conditions increases medication expenses and healthcare utilization. The indirect economic consequences of polypharmacy in cancer care are reflected in productivity losses.

Keywords: *Polypharmacy, Deprescribing, Economy, Cancer, Drugs Interaction.*

Introduction

Increasing survival amongst cancer patients is expected to result in inevitable rise in longevity related morbidities as reported from other diseases states [1]. Increasing medication is unfortunately an inevitable consequence of reducing mortality [2,3]. Polypharmacy refers to the concurrent use of multiple medications, and represent a common practice in the management of cancer patient [4]. Although there is unanimity amongst patients in the general regarding the exact medication thresholds that qualifies for definition of polypharmacy [1], recent studies have raised concerns regarding the discriminative value of this thresholds in some other patient populations with increasing number of life prolonging drugs; such as patients with heart failure or chronic liver disease [5,6]. In patients with different cancer related morbidities, the complexity of their treatment regimens, presence of other comorbidities, and the ever present need for supportive care have all been shown to contribute to the increased use of multiple drugs [4]. While the original intention of multiple medications is to optimize treatment outcomes and address the long-term effects of cancer, it inadvertently also carries significant economic implications for both individuals and healthcare systems. The latter made more apparent since the onset of COVID-19 pandemic; due primarily to competing health costs [7]. In addressing the economic impact of bludgeoning polypharmacy on cancer survivors, it will be appropriate to examine this against differences in access to resources, as well as differences in health systems amongst others. In this perspective, we have examined the key themes driving the economic impact of polypharmacy in this cohort of patients. This monograph provides an overview of the economic impact of polypharmacy among cancer patient survivors, highlighting the direct costs associated with medication use, healthcare utilization, and the indirect costs related to productivity losses. Polypharmacy in cancer survivorship leads to increased direct costs, primarily driven by higher medication acquisition expenses. Cancer treatments, supportive medications, and drugs for managing comorbidities can be costly, especially when multiple medications are prescribed simultaneously [8]. Additionally, some medications may have limited insurance coverage, resulting in substantial out-of-pocket expenses for patients. These medication-related costs contribute to the economic burden faced by cancer patient survivors. Polypharmacy can also lead to

increased healthcare utilization and associated costs. Adverse drug events, drug interactions, and treatment-related complications are more prevalent in patients receiving multiple medications, necessitating hospitalizations, emergency department visits, and outpatient care [8]. The costs associated with these healthcare services and procedures add to the economic impact of polypharmacy among cancer patient survivors.

Furthermore, cancer survivorship often involves the management of long-term effects and chronic conditions resulting from cancer treatments and the aging process. Polypharmacy in managing these late effects and chronic conditions can further contribute to the economic burden. For instance, certain cancer treatments may increase the risk of cardiovascular disease, osteoporosis, and secondary malignancies. The addition of multiple medications to manage these conditions can lead to increased medication expenses and healthcare utilization, impacting the overall economic costs of polypharmacy. Moreover, polypharmacy can have indirect economic consequences through productivity losses among cancer patient survivors. Medication-related side effects, physical limitations, and the complexity of managing multiple medications can affect individuals' ability to work or engage in daily activities. Absenteeism, reduced productivity, and disability can lead to economic burdens not only for the individuals but also for society. These productivity losses can result in decreased workforce productivity and increased social welfare costs [9].

Direct Healthcare Costs

Cost incurred by medication procurement in cancer survivors is a factor of both medications primarily used for cancer therapies as well as other medications that are inevitably critical to the management of concomitant morbidities. The use of these multiple medications may therefore incur higher medication acquisition costs, require more frequent monitoring and laboratory tests (where applicable such as warfarin), and additional healthcare visits to manage medication-related adverse events or drug-drug interactions. The cumulative effect of these factors can significantly impact healthcare expenditures [10]. In addition to medication acquisition costs, frequent monitoring and laboratory tests are often necessary in polypharmacy regimens. These tests are conducted to assess treatment response, monitor potential side effects, and evaluate and calibrate drug-drug interactions (where they occur). The increased need for monitoring can lead to additional healthcare visits and diagnostic procedures, resulting in increased healthcare expenditures. For instance, regular blood tests to assess liver function or hematological parameters may be required for patients receiving certain chemotherapy regimens, adding to the overall healthcare costs. Despite these however, a determination of necessary and unnecessary healthcare costs that is attributable to appropriate and inappropriate polypharmacy remains to be determined.

Furthermore, targeted therapies and immunotherapies, which have revolutionized cancer therapeutics with rising survival matrices and quality adjusted life years (QUALY), tend to be costly with variable affordability across healthcare systems [11]. When multiple drugs are combined in various treatment regimen, the cumulative cost can be substantial, putting inevitable strain on healthcare budgets and potentially affecting patient access to these treatments [10,6].

Cancer therapeutics in particular is inherently prone to various phenotypes of adverse drugs reactions. Factors predisposing to these are beyond the scope of this review and have been exhaustively discussed elsewhere. But in brief, differences in genes encoding proteins involved in the bio-disposition of cancer chemotherapeutics agents meant that these drugs when combined with other drug in treatment regimens readily predispose to various drug-drug and drug-food, pharcogenetic interactions with downstream consequence of ADRs. The management of these medication-related adverse events or drug interactions undoubtedly leads to further increase in healthcare costs. Additionally, Polypharmacy increases the risk of adverse drug events (ADEs), which may require hospitalizations, emergency department visits, or prolonged inpatient medical care. The costs associated with hospital stays, diagnostic evaluations, and additional treatments for managing ADEs can have a substantial impact on healthcare expenditures. Several studies have highlighted the economic implications of polypharmacy in cancer care. For example, Bapat et al's., [8] examination of the direct healthcare costs associated with polypharmacy in cancer patients found that polypharmacy was associated with higher healthcare costs due to increased medication acquisition costs and additional healthcare visits for monitoring and managing drug-related issues. Other factors predisposing to these rising health care costs included drug adherence/concordance. Previous reports have consistently reported on the impact of poor medication ad-

herence, which is often influenced by polypharmacy, on healthcare costs [12]. Non-adherence to prescribed drugs can result in disease progression and the need for more intensive and expensive therapies. It can potentially also contribute to increased healthcare resource utilization, including emergency department visits and unscheduled hospitalizations; inevitably leading to higher healthcare expenditures [14].

To address the economic impact of polypharmacy, optimizing medication management practices is crucial. Strategies such as medication reconciliation, deprescribing when appropriate, and patient education on adherence and potential side effects can help improve patient outcomes and reduce healthcare costs. For instance, a study by Tjia et al. [13] demonstrated that a pharmacist-led medication management intervention reduced the number of potentially inappropriate medications and resulted in cost savings in elderly cancer patients.

Treatment Compliance and Effectiveness

Poor medication adherence, which can be influenced by polypharmacy, may lead to reduced treatment effectiveness and potentially higher healthcare costs. If patients do not adhere to prescribed medications, it may result in disease progression, increased healthcare utilization, and the need for more intensive and expensive treatment options.

Treatment compliance and effectiveness are crucial considerations in cancer care, especially in the context of polypharmacy. Poor medication adherence can have significant implications for patient outcomes and healthcare costs. When cancer patients do not adhere to prescribed medications, it may lead to reduced treatment effectiveness and potentially higher healthcare utilization. In the context of supportive medications, non-adherence can also have adverse consequences. For instance, cancer patients may be prescribed medications to manage treatment-related side effects, such as antiemetics for chemotherapy-induced nausea and vomiting. Where patients do not consistently take these medications as prescribed, inevitable adverse effects may ensue, leading to decreased quality of life and increased healthcare utilization. Uncontrolled symptoms may require additional medical interventions, such as emergency department visits or hospitalizations, to manage the adverse effects, resulting in higher healthcare costs.

Unlike other clinical risks, the economic impact of poor medication adherence in cancer therapeutics can extend beyond the direct costs of healthcare utilization. For example, if treatment effectiveness is compromised due to non-adherence, patients may require longer or more aggressive treatment courses, leading to increased healthcare resource utilization and costs. Additionally, poor adherence can contribute to treatment delays or interruptions, potentially impacting overall treatment outcomes and necessitating adjustments to treatment plans, which may have financial implications [15,16]. Several studies have examined the relationship between medication adherence and treatment outcomes in cancer patients. For instance, McCowan et al.'s, [15] exploration of the impact of adherence to endocrine therapy in breast cancer patients reported that poor adherence was associated with an increased risk of disease recurrence and mortality. This report is consistent with outcome reported by lash et al., on examination of the relationship between medication adherence and survival in colorectal cancer patients. These undoubtedly highlight the importance of medication adherence in optimizing treatment effectiveness and patient outcomes in these cohorts of patients.

Productivity Losses

Polypharmacy in cancer care can have indirect economic consequences through productivity losses. Medication-related side effects and the challenges of managing complex medication regimens can impact cancer patients' ability to work or engage in daily activities. As a result, they may require additional time off work, reduced work hours, or even temporary or permanent disability leave, leading to productivity losses for both the individual and their employer. This often led to absenteeism, reduced productivity, and disability with resulting increase in economic burden for individual patients, and society at large. Ab initio, studies have already shown substantial productivity losses amongst patients on cancer care. De Boer et al's. [17] examination of the productivity costs associated with cancer survivors found substantial proportion of productivity losses amongst cancer survivors; often traceable to absenteeism and reduced work productivity. Other studies have explored functional limitations; albeit with same result on productivity losses [18]. Often the indirect economic impact of all these polypharmacy-related productivity losses extends beyond the individual level. Society as a whole inevitably also bears the economic burden, as reduced productivity among cancer patients can result in lower overall workforce productivity, increased healthcare utilization, and higher social welfare costs.

Addressing productivity losses in cancer care requires a multifaceted approach. Generic interventions such as optimizing medication management to minimize medication-related side effects and promote medication adherence are essential. Supportive interventions, such as workplace accommodations and flexible work arrangements, can help individuals with cancer manage their treatment and work responsibilities more effectively. Additionally, providing psychosocial support and resources to enhance overall well-being can contribute to better productivity outcomes.

Optimization of Medication Management:

Efforts to optimize medication management in cancer care can help mitigate the economic impact of polypharmacy. This includes personalized approaches, such as medication reconciliation, deprescribing when appropriate, and patient education on adherence and potential side effects. Implementing strategies to minimize unnecessary or ineffective medications and manage drug interactions can help improve patient outcomes and reduce healthcare costs. One crucial aspect of optimizing medication management is medication reconciliation. Medication reconciliation involves a comprehensive review and documentation of a patient's medication regimen to ensure accurate and up-to-date information. This process helps identify potential drug interactions, duplicate therapies, or medications that may no longer be necessary. By reconciling medications across different healthcare settings and involving patients in the process, medication-related errors can be minimized, leading to improved patient safety and potentially reducing healthcare costs. In a study by Boockvar et al. [19] medication reconciliation programs were associated with reduced adverse drug events and healthcare utilization.

Additionally, Deprescribing, the process of carefully discontinuing medications that may be unnecessary, ineffective, or harmful, represent another important strategy to optimize medication management [20]. This approach involves regular review of the patient's medication regimen, considering factors such as the patient's current health status, treatment goals, and potential drug interactions. By deprescribing when appropriate, clinicians can minimize polypharmacy, reduce the risk of adverse drug events, and potentially lower healthcare costs. These favorable outcomes have already been explored by a systematic review which showed that deprescribing interventions in older adults resulted in reduced medication use, improved patient outcomes, and potential cost savings [20].

Patient education also plays a vital role in optimizing medication management in these cohorts of patients. By providing clear and concise information to patients about their medications, (including the importance of adherence, potential side effects, and strategies for managing side effects), healthcare providers can improve medication understanding and adherence rates. Effective patient education programs have been shown to enhance medication adherence and reduce the risk of medication-related complications in cancer patients [21].

Moreover, the integration of clinical decision support systems (CDSS) into electronic health records can aid in optimizing medication management. CDSS provides healthcare professionals with real-time, evidence-based recommendations and alerts regarding potential drug-drug interactions, dosing adjustments, or contraindications. By leveraging technology to support medication decision-making, healthcare providers can enhance patient safety, reduce medication-related errors, and improve healthcare resource utilization. A study by Redmond et al. [22] highlighted the effectiveness of CDSS in improving medication safety in cancer care.

In conclusion, optimizing medication management in cancer care through personalized approaches, medication reconciliation, deprescribing when appropriate, patient education, and the integration of clinical decision support systems can help mitigate the economic impact of polypharmacy. By minimizing unnecessary or ineffective medications, managing drug interactions, and promoting medication adherence, healthcare providers can improve patient outcomes, enhance patient safety, and potentially reduce healthcare costs.

The effect of differences in healthcare systems on economic burden of polypharmacy

Fee-for-Service Model

In this model, healthcare providers are reimbursed for each service provided. This payment structure may inadvertently incentivize overutilization of medications, leading to increased polypharmacy and associated costs. The economic burden of polypharmacy in cancer patients is likely to be higher in fee-for-service systems due to the financial incentives for prescribing and administering more medications.

Managed Care Model
Managed care models, such as Health Maintenance Organizations (HMOs), emphasize cost-effective healthcare delivery. These systems often employ utilization management strategies, formularies, and prior authorization requirements to control medication utilization and associated costs. The economic burden of polypharmacy may be relatively lower in managed care models due to their focus on cost containment. This however would need exploration by future prospective studies.

Single-Payer System
In a single-payer system, the government acts as the sole insurer. These systems can negotiate drug prices and have the potential to reduce medication costs through bulk purchasing and centralized decision-making. These are the models in the Gulf cooperation council (GCC) countries. The economic burden of polypharmacy may be mitigated in single-payer systems due to their ability to negotiate favorable prices for medications.
Out-of-Pocket Payments
Healthcare systems with high out-of-pocket payments can impose a significant economic burden on cancer patients using polypharmacy. Patients may face substantial medication costs, leading to medication non-adherence and potentially compromising treatment outcomes.

Insurance Coverage
Healthcare systems that provide comprehensive insurance coverage, including medication benefits, can alleviate the economic burden of polypharmacy in cancer patients. Adequate coverage ensures patients have access to necessary medications without incurring substantial out-of-pocket expenses, reducing financial barriers to adherence and optimal treatment outcomes.

Mixture of private and public payers
The U.S. healthcare system, characterized by a mixture of private and public payers, and often faces dynamic challenges in controlling medication costs. High drug prices and insurance coverage variations contribute to the economic burden of polypharmacy, with patients often shouldering significant out-of-pocket expenses.

United Kingdom
The National Health Service (NHS) in the UK provides comprehensive coverage, including cancer medications. This system employs cost-effectiveness assessments and centralized purchasing to manage medication costs, reducing the economic burden on patients and the healthcare system.
Differences in healthcare systems significantly influence the economic burden of polypharmacy in cancer patients. Fee-for-service models, high out-of-pocket payments, and limited medication access can increase the economic burden, while managed care models, comprehensive insurance coverage, and cost-containment strategies can help mitigate it. By understanding these differences, policymakers and healthcare providers can develop strategies to optimize medication management, minimize the economic burden, and improve patient outcomes.

CONCLUSION AND FUTURE PERSPECTIVES

It is important to note that the economic impact of polypharmacy in cancer care can vary based on factors such as healthcare systems, insurance coverage, medication pricing, and patient-specific factors. Conducting economic evaluations and cost-effectiveness studies specific to different healthcare settings and cancer populations can provide further insights into the financial implications of polypharmacy and help inform decision-making processes.

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