Medication Regimen Complexity Index On Geriatric COPD Patients

Pavitra*[1], Robin George[2], Rashmi G[1]
[1] *M PHARM, Department of Pharmacy Practice, Sri Adichunchanagiri Hospital and Research Centre, Mandya, India*
[2]*Assistant Professor, Department of Pharmacy Practice, Sri Adichunchanagiri College of Pharmacy, Mandya, India.*

ABSTRACT: COPD remains a global health concern, with declining death rates, yet it is poised to become the third most prevalent cause of mortality worldwide by 2030, with smoking being the most common risk factor. The treatment of COPD involves the use of nebulizers, spacers, inhalers, and tablets; employing these medications increases the complications, this study deals with the multiple medication complications among geriatric COPD patients by using the MRCI scale. patients can manage their symptoms more effectively and improve their complications. This study analyzed 40 articles based on inclusion and exclusion criteria, out of 6 selected from 40. The study highlights the complexity of COPD medication, Dosing frequency, and additional instructions were medication regime complexity index components that most contributed to the high complexity of the medication regimen. Drug interactions and errors can significantly impact a patient's health, especially in managing conditions like COPD. Pharmacists are essential in reducing these risks by thoroughly evaluating a patient's medication regimen, considering the number of medications, dosages, and frequency of use. By identifying potential interactions and simplifying the medication regimen, pharmacists can help reduce the complexity of managing the disease. This not only improves patient outcomes but also decreases the risk of adverse events potentially lowers mortality rates and increases adherence.

KEYWORDS: COPD, MRCI, GOLD, FVI.

INTRODUCTION

COPD

COPD (Chronic Obstructive Pulmonary Disease) is a common lung disease that makes it hard to breathe and restricts airflow. Unlike asthma, where airflow obstruction can often be reversed with treatment, COPD progresses slowly and is not easily reversible. Factors such as long-term exposure to tobacco smoke, ongoing inflammation throughout the body, and lack of physical activity contribute to the development and worsening of COPD. These factors also increase the likelihood of other health issues occurring alongside COPD, known as comorbidities. (1)

COPD is a condition where airflow in the lungs is restricted and cannot be fully reversed, as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD).(2) Airflow restriction in COPD typically worsens over time and is linked to abnormal lung inflammation triggered by harmful particles and gases.(3)(4)(5)(6)(7) The Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD is a common, treatable, and preventable condition that limits airflow in the lungs and tends to worsen over time.(8) COPD is also linked to increased inflammation in the airways and lungs. It leads to a significant number of deaths and places a heavy financial burden on healthcare systems. (9)(10) (4)(11)(5)

Even though death rates are decreasing, COPD remains one of the leading causes of mortality worldwide. Other health conditions that occur alongside COPD worsen its outlook and symptoms, adding to the overall burden of the disease. (11)(2)(1) According to GOLD, obstructive lung disease is diagnosed when the FEV1/FVC ratio is 70% or lower after bronchodilator therapy. The severity of airflow limitation is classified based on the percentage of FEV1 compared to the predicted value. Because symptoms often don't show up until the disease is severe, many people are diagnosed and treated for COPD at an advanced stage. (12)

COMPLEXITY OF COPD TREATMENT

The 2018 GOLD guideline paper offers therapy recommendations for COPD based on different phenotypes identified by symptoms and previous exacerbations. (13) The treatment standards for

COPD include bronchodilators, particularly dual therapy with both long-acting anticholinergics (LAMA) and long-acting beta-agonists (LABA). This approach is increasingly favored as studies suggest that LAMA/LABA combinations improve lung function and symptoms without increasing risks compared to using LAMA or LABA alone. (13) Consistent and regular medication use is crucial in treating COPD. However, many COPD patients struggle with adherence to their inhaled treatments, with only about half taking their medication as prescribed due to complexity. (14) Because COPD is a complex illness with diverse symptoms, developing a staging method for it poses challenges in establishing treatment plans and assessing the severity of the condition. (15). Therapies for COPD can reduce the frequency and severity of exacerbations, improve symptoms, and overall health, and increase activity levels. (2), (15)

NEED TO ASSESS AND REDUCE COMPLEXITY

In the curable traits approach, each patient with chronic airway disease undergoes a multidimensional assessment to identify core qualities linked to illness outcomes. Based on this evaluation, targeted, evidence-based treatments are applied. Three domains - pulmonary, extrapulmonary, and Behavioral/risk factors - categorize traits. The assessment includes the patient's clinical history, risk factors, exposures, and objective measurements like spirometry, blood eosinophil counts, and exhaled nitric oxide fraction (FENO). The first step aims to determine if the patient has airway disease, providing a probability - high or low - of its presence. If airway disease is highly likely, manageable qualities are analyzed, and treatment is tailored accordingly. (16)

Numerous well-documented barriers to medication adherence exist, such as high costs, limited health literacy, and concerns about medications. Another significant factor contributing to low adherence rates is the complexity and number of medications in a patient's regimen. Over three-quarters of COPD patients have four or more additional chronic conditions, which can make managing and taking multiple medications overwhelming and lead to underuse.(14) Reducing the complexity of medication regimens in geriatric COPD patients is essential. Simplifying medications makes adherence easier, leading to better treatment outcomes. Due to the reason of causing adverse events, drug-drug interaction, and multiple use of drugs.

POLYPHARMACY IN COPD PATIENT

Polypharmacy in COPD patients, the use of multiple medications, is common among older adults and has been linked to various negative outcomes. These include poorer medication adherence, longer hospital stays, inappropriate prescribing, increased risk of adverse drug reactions, and a higher likelihood of drug interactions. (17)(18). While there's no universally agreed-upon threshold, many consider the regular use of five or more medications to constitute COPD with comorbidities. This includes prescription drugs, over-the-counter medications, as well as standard and complementary medicines that a patient may be using. (19)

Polypharmacy in COPD refers to the simultaneous use of multiple medications like nebulizers, spacers, inhalers, tablets, and other medications which increases the medication complexity in COPD. (17)(20) Typically, a threshold of five or more medications is used to distinguish polypharmacy. (21) Polypharmacy in COPD is frequently observed to rise with increasing age. (22) Older individuals experience changes in both pharmacokinetics and pharmacodynamics, making them more susceptible to adverse effects from medications. Additionally, the growing number of COPD and comorbidities in this population further increases their vulnerability to medication-related issues. (23)

While polypharmacy is acknowledged as a risk factor for adverse drug reactions, drug-drug interactions, and medication non-adherence, it is also believed to provide substantial health benefits for many individuals with COPD and various diseases. (24)(22)(25)(26)(27)

GERIATRIC PATIENT WITH COPD

Comorbidity is common among individuals aged 65 and older, with estimates suggesting that 55% to 98% of elderly people have more than one chronic illness. (28), Treating patients with long-term health issues can become more complex when they take multiple medications. This complexity arises from various factors, including different dosage forms, dosing frequencies, and additional regimen directions if necessary. (29) Older adults may find taking medications challenging due to the complexity of their medication regimens. (30)

In Germany, the incidence of COPD is 5.7% among individuals aged 45 to 64 and 11.7% among those

over 64. Men over 64 are more affected than women, similar to younger age groups (12.5% versus 11.0% in Germany). The World Health Organization forecasts that COPD will become the third most common cause of death globally by 2030. Smoking is the primary risk factor for COPD, followed by occupational hazards and pollution. (31)

RISK FACTORS AMONG GERIATRIC PATIENTS WITH COPD

Studies have linked multi-pharmacy to more medication-related issues, such as side effects and drug interactions. (29) Few recent studies have examined risk factors for accidental or inappropriate use of psychotropic drugs at a national level, according to Beer's standards. (32) There's still uncertainty about how excessive mucus production impacts airflow restriction in COPD patients. Recent research suggests that excessive mucus secretion might be a risk factor for a faster decline in lung function, despite earlier studies suggesting it wasn't linked to any physiological defects. (3)

Treating COPD patients at high risk for cardiovascular comorbidities and providing optimal risk management is crucial. Routine cardiovascular examinations should be conducted for all COPD patients, with appropriate addressing of risk factors, even in the absence of specific guidelines for managing cardiovascular risk in COPD. Additionally, during COPD episodes, it's important to assess for concurrent cardiac involvement or differential diagnoses, as these events can increase the risk of cardiovascular disease due to various factors such as inactivity, hypoxia, tachycardia, arterial stiffness, pulmonary hypertension, changes in cardiac function, elevated platelet activation, and the use of high-dose β2 agonists. (11)

In populations with diabetes, younger patients are more likely to be noncompliant, whereas this trend is not observed in those with hypertension. Additionally, age and gender, particularly being female, are persistent and non-modifiable factors associated with low compliance across various conditions. (33) The most well-established risk factor for COPD is indeed personal exposure to tobacco smoke, whether from smoking cigarettes, using water or gas pipes, or combining it with marijuana. However, it's essential to acknowledge that 30% of individuals with COPD in the community have never smoked, underscoring the existence of other substantial risk factors beyond tobacco smoke exposure. (34)

MRCI

Clinical practice guidelines are increasingly advocating the use of multiple medications to achieve therapeutic goals. (35)Older adults may develop complex drug schedules due to this trend. Complexity can arise from different dosage forms, multiple daily doses, and multiple medications. Complicated prescription regimens increase the risk of dosage and administration errors, which could have serious consequences, particularly for individuals using high-risk medications like insulin, warfarin, and opioids. The complexity of a patient's medication regimen may independently contribute to unfavorable outcomes. (26). Furthermore, certain demographics, such as the elderly and individuals with cognitive impairment, may be more prone to making these errors. However, prior research has not explored the connection between the complexity of an older individual's medication regimen and their mortality. (27)

Complexity has been associated with factors such as nonadherence and adverse drug events (ADEs), (36), (37) elderly care facility discharges from hospitals, (38), and readmission to the hospital. (36) Hospitals nationwide are striving to identify readmission risk factors and seeking resources to determine which patients would benefit from targeted interventions. Despite drug-related issues being acknowledged causes of readmission, limited research has explored the link between medication-related risk factors and hospital readmission. (39) In 2008, it was determined that adverse drug reactions might have been responsible for up to 35% of hospital readmissions. (40)

MRCI SCORING HELP IN COPD MEDICATION

The electronic MRC Data Capture Tool and guide, along with MRCI Additional Instructions, were acquired from the University of Colorado and employed to compute MRCI scores. In instances where discrepancies between the MRCI Additional Instructions and its description were apparent, 14 scores were determined using the initial MRCI tool. (40) The study utilized the Medication Regimen Complexity Index (MRCI), a validated measuring instrument consisting of 65 items. This tool can be populated with data extracted from patient medical records, including electronic prescription

information from a drug list. Its purpose was to assess the complexity of medication regimens in COPD patients. (28)

In the Medication Regimen Complexity Index (MRCI), the number of medications, dosage frequency, administration guidelines, and recommended dosage forms are multiplied by corresponding averages to determine complexity levels. However, there are gaps in data collection with MRCI. For instance, many MRCI studies only focus on assessing the complexity of long-term treatment regimens, omitting consideration of other over-the-counter and prescription drugs used for COPD and comorbidities. (41) As a result, comparing the complexity of medication regimens across different disease states becomes challenging. Studies on regimen complexity utilize highly personalized measures, such as the Antiviral Regimen Complexity Index, alongside more general measures like the MRCI. This variation in measurement tools makes direct comparisons difficult. (42)

The MRCI scores serve three primary purposes:
(A) To compare patient-level MRCI scores, encompassing both prescription and over-the-counter medications, across four defined cohorts with prevalent chronic diseases.
(B) To investigate the contributions of medication types (including prescription drugs specific to the disease state defined by the cohort, other prescription drugs, and over-the-counter drugs) and medication regimen characteristics (such as dosage form, dosing frequency, and additional usage directions) to total patient-level MRCI scores.
(C) To assess the association between MRCI scores and objective metrics of patient severity or disease complexity, including medication count, diagnosis measure, and Charlson comorbidity index scores, among other factors. (43) (44)

MATERIALS AND METHODOLOGY

I searched PubMed, Google Scholar, and Medline and found 300 articles. From there, I selected 40, of which 6 were particularly relevant based on their methodology. and observed Inclusion and Exclusion criteria also cover articles of results with significant P-values (P>0.005).

RESULTS

Reference	Country	Sex ratio M: F	Age	Type of Study	Sample size	Number of drugs	Clinical characteristics	MRCI score	P value
Barbara c wimmer et.al.	Australia, 2015	1.38: 1.04	≤ 80 years	Observational	3348	470	Comorbidity Non-comorbidity	> 26	<0.001
Netsanat a negewo et.al.	Australia, 2017	5.86: 0	69.1 years	Cross-sectional study	222	24	comorbidity Non-comorbidity	24(18.5-31)	<0.001
Lais LN Pantuzza et.al.	Japan, 2018	0: 7.09	71.4 years	Cross-sectional study	227	>5	Comorbidity Non-comorbidity	12.0(4.0-35.00)	<0.001
Lais lessa neiva pantuzza et. al.	European, 2019	0: 7.09	70 years	Cross-sectional study	227	>5	Comorbidity Non-comorbidity	20.8	<0.02
Sunmin Lee et. al.	Australia, 2019	5.74: 0	68.7 years	Cross-sectional study (retrospective)	331	6.1±3.3	Comorbidity Non-comorbidity	28.2 ± 14.2 (4-72)	<0.001
Jesus Ruiz Ramos et. al.	Spain, 2020	0: 5.61	>80 years	Observational study	201	9 (6-12)	Comorbidity Non-comorbidity	25(17.5-33)	<0.001

DISCUSSION

The intersection of medication complexity, comorbidities, and patient outcomes is a critical area of research in healthcare, as highlighted by several recent studies. Barbara C. Wimmer et al.'s research underscores the significant impact of complex medication schedules on mortality risk, particularly among older men. They emphasize that complex

regimens increase the likelihood of errors and adverse reactions, leading to higher mortality rates. Practical measures such as simplifying medication plans and reducing unnecessary prescriptions are recommended to mitigate these risks. Policy initiatives promoting regular medication assessments and cognitive evaluations are also advocated to enhance patient outcomes.

This article study delves into the relationship between comorbidities, COPD severity, and medication complexity. They stress the importance of comprehensive indices like the medication regimen complexity Scale (MRCI) in evaluating treatment effectiveness. Elevated MRCI scores in individuals with severe COPD highlight the impact of complex medication regimens on disease management. The study underscores the need for thorough evaluations in COPD management to enhance patient well-being and results, particularly in assessing exacerbation frequency, lung function, and quality of life about medication complexity.

Finally, other article, emphasize the challenges posed by Drug-Related Polypharmacy (DRP), particularly among the elderly with multiple chronic conditions. They highlight the significant contribution of DRPs to emergency department visits and advocate for simplifying treatment through prompt medication review and education. Effective communication with healthcare providers outside the hospital setting is deemed essential for comprehensive patient care.

In summary, these studies collectively underscore the complex relationship between medication complexity, comorbidities, and patient outcomes. They highlight the importance of comprehensive assessments, standardized tools like the MRCI, and policy initiatives aimed at optimizing pharmacotherapy, reducing adverse events, and enhancing patient safety and well-being across diverse healthcare settings.

CONCLUSION

Drug interactions and errors can significantly impact a patient's health, especially in managing conditions like COPD. Pharmacists play a crucial role in minimizing these risks by carefully reviewing a patient's medication regimen, including the number of medications, doses, and frequency of intake. By detecting possible problems and streamlining the pharmaceutical regimen, pharmacists may assist minimize the difficulty of managing the condition. This not only helps patient results but also lessens the likelihood of harmful events perhaps lowers death rates and increases adherence.

REFERANCE

[1]. Noteboom B, Jenkins S, Maiorana A, Cecins N, Ng C, Hill K. Comorbidities and medication burden in patients with chronic obstructive pulmonary disease attending pulmonary rehabilitation. Vol. 34, Journal of Cardiopulmonary Rehabilitation and Prevention. 2014. p. 75–9.

[2]. Negewo NA, Gibson PG, Wark PAB, Simpson JL, McDonald VM. Treatment burden, clinical outcomes, and comorbidities in COPD: An examination of the utility of medication regimen complexity index in COPD. International Journal of COPD. 2017 Oct 6;12:2929–42.

[3]. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: Molecular and cellular mechanisms. Vol. 22, European Respiratory Journal. European Respiratory Society; 2003. p. 672–88.

[4]. Franssen FM, Spruit MA, Wouters EFM. Determinants of polypharmacy and compliance with GOLD guidelines in patients with chronic obstructive pulmonary disease. International Journal of COPD. 2011;6(1):493–501.

[5]. Liu Z, Lin L, Liu X. Clinical application value of impulse oscillometry in geriatric patients with COPD. International Journal of COPD. 2017 Mar 15;12:897–905.

[6]. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Am J Respir Crit Care Med. 2023 Apr 1;207(7):819–37.

[7]. Annegarn J, Meijer K, Passos VL, Stute K, Wiechert J, Savelberg HHCM, et al. Problematic Activities of Daily Life are Weakly Associated With Clinical Characteristics in COPD. J Am Med Dir Assoc. 2012;13(3):284–90.

[8]. Hillas G, Perlikos F, Tsiligianni I, Tzanakis N. Managing comorbidities in COPD. Vol. 10, International Journal of COPD. Dove Medical Press Ltd.; 2015. p. 95–109.

[9]. Decramer M, Janssens W. Chronic obstructive pulmonary disease and comorbidities. Vol. 1, The Lancet Respiratory Medicine. 2013. p. 73–83.

[10]. Mannino DM, Higuchi K, Yu TC, Zhou H, Li Y, Tian H, et al. Economic burden of COPD in the presence of comorbidities. Chest. 2015 Jul 1;148(1):138–50.

[11]. Vanfleteren LEGW, Spruit MA, Wouters EFM, Franssen FME. Management of chronic obstructive pulmonary disease beyond the lungs. Vol. 4, The Lancet Respiratory Medicine. Lancet Publishing Group; 2016. p. 911–24.

[12]. Neumann N, Odegard P, Swanoski M. New Perspectives Considerations for Geriatric Patients with COPD. Vol. 33. 2018.

[13]. Candela M, Costorella R, Stassaldi A, Maestrini V, Curradi G. Treatment of COPD: The simplicity is a resolved complexity. Multidiscip Respir Med. 2019 Jun 3;14(1).

[14]. Federman AD, O'conor R, Wolf MS, Wisnivesky JP. Associations of medication regimen complexity with copd medication adherence and control. International Journal of COPD. 2021;16:2385–92.

[15]. Högman M, Sulku J, Ställberg B, Janson C, Bröms K, Hedenström H, et al. 2017 global initiative for chronic obstructive lung disease reclassifies half of COPD subjects to lower risk group. International Journal of COPD. 2018;13:165–73.

[16]. Duszyk K, McLoughlin RF, Gibson PG, McDonald VM. The use of treatable traits to address COPD complexity and heterogeneity and to inform the care. Breathe. 2021 Dec 1;17(4).

[17]. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in Elderly Patients. The American Journal of Geriatric Pharmacotherapy. 2007.

[18]. Onder G, Liperoti R, Foebel A, Fialova D, Topinkova E, Van der Roest HG, et al. Polypharmacy and mortality among nursing home residents with advanced cognitive impairment: Results from the shelter study. J Am Med Dir Assoc. 2013;14(6):450.e7-450.e12.

[19]. Pazan F, Wehling M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. Vol. 12, European Geriatric Medicine. Springer Science and Business Media Deutschland GmbH; 2021. p. 443–52.

[20]. Abdelbary A, Kaddoura R, Balushi S Al, Ahmed S, Galvez R, Ahmed A, et al. Implications of the medication regimen complexity index score on hospital readmissions in elderly patients with heart failure: a retrospective cohort study. BMC Geriatr. 2023 Dec 1;23(1).

[21]. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, et al. Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol. 2012 Sep;65(9):989–95.

[22]. Hovstadius B, Hovstadius K, Åstrand B, Petersson G. Increasing polypharmacy - an individual-based study of the Swedish population 2005-2008. BMC Clin Pharmacol. 2010 Dec 2;10.

[23]. Turnheim K. When drug therapy gets old: Pharmacokinetics and pharmacodynamics in the elderly. Vol. 38, Experimental Gerontology. Elsevier Inc.; 2003. p. 843–53.

[24]. Bjerrum L, Rosholm JU, Hallas J, Kragstrup J. PHARMACOE PIDEMIOLOGY AND PRESCRIPTION Methods for estimating the occurrence of polypharmacy by means of a prescription database.

[25]. Gorard DA. Escalating polypharmacy. QJM. 2006 Nov;99(11):797–800.

[26]. Charlesworth CJ, Smit E, Lee DSH, Alramadhan F, Odden MC. Polypharmacy among adults aged 65 years and older in the United States: 1988â€"2010. Vol. 70, Journals of Gerontology - Series A Biological Sciences and Medical Sciences. Oxford University Press; 2015. p. 989–95.

[27]. Wimmer BC, Bell JS, Fastbom J, Wiese MD, Johnell K. Medication Regimen Complexity and Polypharmacy as Factors Associated With All-Cause Mortality in Older People: A Population-Based Cohort Study. Annals of Pharmacotherapy. 2016 Feb 1;50(2):89–95.

[28]. Wimmer BC, Cross AJ, Jokanovic N, Wiese MD, George J, Johnell K, et al. Clinical Outcomes Associated with Medication Regimen Complexity in Older People: A Systematic Review. J Am Geriatr Soc. 2017 Apr 1;65(4):747–53.

[29]. Lee S, Jang JY, Yang S, Hahn J, Min KL, Jung E hee, et al. Development and validation of the Korean version of the medication regimen complexity index. PLoS One. 2019 May 1;14(5).

[30]. Linnebur SA, Vande Griend JP, Metz KR, Hosokawa PW, Hirsch JD, Libby AM. Patient-level medication regimen complexity in older adults with depression. Clin Ther. 2014 Nov 1;36(11):1538-1546.e1.

[31]. Luley MC, Loleit T, Knopf E, Djukic M, Criée CP, Nau R. Training improves the handling of inhaler devices and reduces the severity of symptoms in geriatric patients suffering from chronic-obstructive pulmonary disease. BMC Geriatr. 2020 Oct 9;20(1).

[32]. Aparasu RR, Mort JR. Prevalence, Correlates, and Associated Outcomes of Potentially Inappropriate Psychotropic Use in the Community-Dwelling Elderly. Vol. 2, Am J Geriatr Pharmacother. 2004.

[33]. Corsonello A, Pedone C, Lattanzio F, Lucchetti M, Garasto S, Carbone C, et al. Regimen complexity and medication nonadherence in elderly patients [Internet]. Therapeutics and Clinical Risk Management. 2009. Available from: https://www.dovepress.com/

[34]. Lõpez-Campos JL, Tan W, Soriano JB. Global burden of COPD. Vol. 21, Respirology. Blackwell Publishing; 2016. p. 14–23.

[35]. Hughes LD, McMurdo MET, Guthrie B. Guidelines for people not for diseases: The challenges of applying UK clinical guidelines to people with multimorbidity. Age Ageing. 2013 Jan;42(1):62–9.

[36]. Willson MN, Greer CL, Weeks DL. Medication Regimen Complexity and Hospital Readmission for an Adverse Drug Event. Annals of Pharmacotherapy. 2014 Jan;48(1):26–32.

[37]. de Vries ST, Keers JC, Visser R, de Zeeuw D, Haaijer-Ruskamp FM, Voorham J, et al. Medication beliefs, treatment complexity, and non-adherence to different drug classes in patients with type 2 diabetes. J Psychosom Res. 2014 Feb;76(2):134–8.

[38]. Wimmer BC, Dent E, Visvanathan R, Wiese MD, Johnell K, Chapman I, et al. Polypharmacy and medication regimen complexity as factors associated with hospital discharge destination among older people: A prospective cohort study. Drugs Aging. 2014;31(8):623–30.

[39]. Ruiz B, García M, Aguirre U, Aguirre C. Factors predicting hospital readmissions related to adverse drug reactions. Eur J Clin Pharmacol. 2008 Jul;64(7):715–22.

[40]. Abou-Karam N, Bradford C, Lor KB, Barnett M, Ha M, Rizos A. Medication regimen complexity and readmissions after hospitalization for heart failure, acute myocardial infarction, pneumonia, and chronic obstructive pulmonary disease. SAGE Open Med. 2016;4.

[41]. Stange D, Kriston L, Langebrake C, Cameron LK, Wollacott JD, Baehr M, et al. Development and psychometric evaluation of the German version of the Medication Regimen Complexity Index (MRCI-D). J Eval Clin Pract. 2012 Jun;18(3):515–22.

[42]. DiIorio C, McDonnell M, McCarty F, Yeager K. Initial testing of the antiretroviral medication complexity index. Journal of the Association of Nurses in AIDS Care. 2006;17(1):26–36.

[43]. Mansur N, Weiss A, Beloosesky Y. Looking beyond polypharmacy: Quantification of medication regimen complexity in the elderly. American Journal of Geriatric Pharmacotherapy. 2012 Aug;10(4):223–9.

[44]. Libby AM, Fish DN, Hosokawa PW, Linnebur SA, Metz KR, Nair K V., et al. Patient-Level Medication Regimen Complexity Across Populations With Chronic Disease. Clin Ther. 2013;35(4).