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A Comprehensive Examination of Drug-Drug and Drug-Disease Interactions in Polypharmacy: Implications for Diagnostic Imaging Outcomes in Middle-Aged and Older Adults

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Abstract

Background: The prevalence of multimorbidity among the elderly population has led to increased instances of polypharmacy, which significantly raises the risk of drug-drug interactions (DDIs) and drug-disease interactions (DDIs). These interactions can adversely affect patient outcomes, particularly in diagnostic imaging settings.

Methods: This systematic review sought to evaluate the relationship between drug-disease interactions and the risk of hospitalization and mortality in middle-aged and older adults. A comprehensive search was conducted across multiple databases, including MEDLINE, CINAHL, EMBASE, and others, to identify relevant studies published up to 2023. The review focused on studies that examined inappropriate prescriptions and their implications for patient health outcomes.

Results: The findings reveal a notable correlation between specific drug-disease interactions and increased risks of hospitalization and mortality. For instance, the concurrent use of certain antihypertensives in frail elderly patients was associated with a heightened risk of adverse events. However, the review also highlighted a lack of standardized definitions for drug-disease interactions, which complicates the comparison of outcomes across studies.

Conclusion: The existence of drug-disease interactions is a significant concern in managing patients with multimorbidity, particularly in hospital settings. This review underscores the urgent need for standardized criteria to identify and manage these interactions effectively. Future research should focus on developing targeted interventions to mitigate the risks associated with polypharmacy, ultimately improving patient safety and outcomes in clinical practice.

Keywords: Multimorbidity, polypharmacy, drug-disease interactions, patient outcomes, systematic review.

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1. Introduction

Multimorbidity, characterized by the coexistence of two or more chronic health disorders, affects more than 50% of the elderly population [1-3]. Multimorbidity is acknowledged as a contributing cause to the

increasing rates of hospitalizations and death. Hospitalized patients often exhibit multimorbidity and have a heightened risk of improper prescription (IP), including drug-disease interactions [4-6]. Drug-disease interactions often occur in 6–30% of community-dwelling elderly people and 15% of fragile older adults upon hospital discharge [7,8]. Research conducted in a hospital environment identified the most prevalent drug-disease interactions as the administration of first-generation calcium channel blockers to individuals with congestive cardiovascular failure and the use of aspirin in individuals with chronic peptic ulcer disease [9]. Hospitalization may provide an opportunity to optimize prescription for persons with multimorbidity and enhance health outcomes.

Drug-disease interactions often arise when a medication intended for one ailment aggravates an existing medical condition. Despite the existence of this broad definition, standardized criteria for drug-disease interactions have not been established, unlike those produced for possibly inappropriate medications in the elderly. Interactions between drugs and diseases may arise from conflicts linked to treatment medications, which are increasingly acknowledged in populations with multiple comorbidities [10-13]. Despite the little research on drug-disease interactions, about fifty percent of elderly individuals with cardiovascular disease have a medication-related conflict. Examples include the use of corticosteroids for sudden flares of persistent obstructive pulmonary disease and non-steroidal anti-inflammatory medicines for pain, both of which are linked to the exacerbation of heart failure [12]. Specific drug-disease interactions have been demonstrated shown to correlate with negative outcomes in the community context. The simultaneous use of corticosteroids in patients with diabetes mellitus and persistent obstructive pulmonary disease correlates with a heightened risk of diabetes-related hospitalization [14].

A potential cause for these drug-disease conflicts is that the research supporting the assumed hazards and benefits of medications may not be applicable to individuals with multimorbidity. Guideline recommendations are often formulated based on short-term randomized controlled studies focused on individual disease states [15, 16]. While a particular patient meta-analysis indicated that the therapeutic benefit of medications was consistent regardless of comorbidity, the majority of multimorbid people are barred from clinical trials, raising uncertainty about the generalizability of the results to this expanding population [17-19]. Observational research using real-world datasets indicate that the risks and advantages of drugs may vary dependent on specific comorbidities, multimorbidity, or frailty.

US observational research indicated that the efficacy of guideline-directed medications for many prevalent chronic illnesses was contingent upon the existing comorbidities [20]. Research in Australia including elderly frail women with acute coronary syndrome indicated that prescribing four guideline-recommended medications correlated with a heightened risk of falls, without the anticipated decrease in cardiovascular events [21]. Adults with cardiac arrest and cognitive impairment exhibited elevated mortality and bleeding rates compared to their non-anticoagulated counterparts. The administration of antihypertensives in community-dwelling persons exhibiting frailty is linked to an elevated risk of adverse effects, with data indicating that greater blood pressure may provide protective benefits [22, 23]. In individuals with weakness, double antiplatelet medication is linked to a heightened risk of adverse events, while statins seem to lack mortality benefits according to a comprehensive assessment of prospective and retrospective trials [24, 25]. A comprehensive knowledge of the hazards and advantages of guideline-directed medications in real-world contexts is essential, particularly concerning the impact of comorbidities, multimorbidity, and frailty. The results of these research are anticipated to influence prescription choices and protocols.

This study included middle-aged individuals, the predominant demographic of individuals with multimorbidity in relative terms, who are prone to encounter drug-disease interactions [26-28]. We concentrated on the hospitalized group, since these patients are anticipated to be at the greatest risk of bad outcomes, and their admission offers a chance to address IP. This systematic review aimed to ascertain the relationship between drug-disease combinations and the likelihood of readmission and death in hospitalized middle-aged and older persons, as well as to evaluate whether therapies targeting drug-disease interactions modify that risk.

2. Search Methodology

A three-step search technique was used to identify published as well as unpublished papers. The terminology in the titles and abstracts of pertinent papers, together with the index terms used to characterize the articles, was utilized to formulate a comprehensive search strategy for the databases to be queried. The databases included MEDLINE (OVID), CINAHL (EBSCO), EMBASE (OVID), Web of Science, SCOPUS, and the Cochrane Library. These datasets were examined from their origin until 2023.

3. The impact of possibly inappropriate prescribing on health outcomes

Multiple papers were discovered that originally seemed to satisfy the inclusion criteria but were subsequently eliminated from the evaluation after the full-text review. The following research exemplify those that have been omitted, accompanied with justifications. Delgado et al. conducted retrospective cohort research to assess the impact of possibly inappropriate prescribing on unfavorable health outcomes [29]. Nevertheless, the patients were situated in a primary care environment rather than being hospitalized; so, this research was omitted due to its inappropriate setting. Wessinger et al. conducted case-controlled research evaluating patients administered selective inhibitors of serotonin reuptake in the context of gastrointestinal hemorrhage, predicated on the hypothesis that this class impairs platelet function and hemostasis [30]. Nevertheless, the research failed to disclose the results of interest, including death or readmissions. Rassen et al. conducted a cohort study examining cardiovascular events and death in individuals with ischemic heart failure or acute coronary syndrome who were administered clopidogrel having proton pump inhibitors [31].

The studies encompassed both male and female participants, with male representation varying from 48% to 57% among the studies, and the mean or median age ranging from 73 to 80 years. Two investigations focused only on older persons, using age cut-offs of 65 and 70 years, correspondingly [32, 33]. Despite two studies including people of various ages, the average age and distribution indicate that few, if any, middle-aged individuals were included [34, 35].

Studies varied about the cohort of hospitalized patients included. Gigante et al. encompassed all hospitalized patients [32]. Bingham et al. included those directed to pharmacy for continuity of medical care [34]. O'Shaughnessy et al. included hospitalized patients with chronic renal disease [35]. Rodighiero et al. considered patients who were hospitalized and were released alive after aortic valve implants [33].

While all studies documented exposure to drug-disease interactions, the methodologies used to delineate this sort of interaction differed across the investigations. Rodighiero et al. employed the MedSafer digital technology, which detected drug interactions and possibly inappropriate medications based on patient-specific comorbidities [33]. This included a subgroup analysis for individuals administered diltiazem with heart failure. Bingham et al. evaluated drug-disease interactions detected by a pharmacist [34]. O'Shaughnessy et al. evaluated non-adherence to guidelines in the Renal Drug Handbook and British National Formulary [35]. Gigante et al. evaluated medications contraindicated due to renal function in accordance with clinical recommendations or product information [32].

Three studies evaluated readmission outcomes [32-34], whereas two examined death rates [32, 35]. Three trials included patients over periods of 6 years [32], 1 year [34], and 6 months [35], accordingly. Rodighiero et al. [33] failed to disclose the length of the trial. The follow-up results differed across the research. Rodighiero et al. evaluated all-cause hospital readmissions with a follow-up period of 30 days, however it was ambiguous whether this interval started from the time of enrollment, aortic valve replacement, or release [33]. Bingham et al. evaluated hospital readmissions within 30 days post-discharge [34]. O'Shaughnessy et al. evaluated mortality one-year post-assessment for drug-disease interactions [35]. Gigante et al. evaluated all-cause mortality, heart disease readmissions, and cardiovascular readmissions, along with a composite death rate and readmission or heart attack and readmission. Outcomes were evaluated with follow-up at 3 months post-discharge from 2010 to 2016 and at 12 months post-discharge from 2012 to 2016 [32].

4. Correlation of Drug-Disease Interactions with Readmission Rates and Mortality

Two investigations demonstrated a correlation between drug-disease interactions and death or hospitalizations [32, 33]. Rodighiero et al. conducted a retrospective cohort analysis including patients aged ≥70 years who left the hospital alive following the completion of transcatheter or surgical replacement of the aortic valve at two university hospitals [33]. The research indicated that the concomitant use of diltiazem with heart failure significantly elevated the probability of readmission within 30 days. Bingham et al. evaluated the risk of drug-disease interactions in persons assigned for change of care services who had a pharmacist evaluation [34]. Drug-disease interactions weren't linked with hospitalizations within 30 days post-discharge. O'Shaughnessy et colleagues. evaluated non-adherence to dose guidelines in the Renal Drug Handbook or British National Formulary among hospitalized patients with chronic renal disease [35]. No difference in mortality was seen at one-year post-assessment between individuals exposed and unexposed to drug-disease interactions.

Gigante et al. evaluated the administration of medications contraindicated due to renal function, in accordance with clinical recommendations and product information, for the chronic diseases of diabetes, hypertension, atrial fibrillation, cardiovascular disease, and prolonged heart failure [32]. The administration of medications prohibited based on renal function correlated with a heightened risk of all-cause mortality and a composite outcome of any mortality or rehospitalization. In contrast, no correlation was found between this IP and cardiovascular mortality, heart readmission, or a composite of cardiovascular mortality or readmission. There were no studies that examined outcomes for middle-aged adults subjected to drug–disease interactions.

Although multimorbidity is common among hospitalized people, there is a scarcity of research investigating the risk of drug-disease interactions and their association with death or readmission in this population. Two investigations identified an elevated risk of hospitalizations or death in hospitalized elderly patients exposed to two particular kinds of drug-disease interactions. This pertains to the administration of diltiazem in patients with cardiac failure and the use of medications prohibited due to renal function. Nonetheless, the meta-analysis revealed no correlation between drug-disease interactions and readmissions among older persons. The lack of a standardized definition for drug-disease interactions is a drawback in the literature in this domain. The empirical investigations reported in research were susceptible to bias, often due to insufficient identification and correction for variables. Additional investigation into drug-disease interactions and poor consequences is essential due to the increasing frequency of multiple medical conditions and polypharmacy alongside an aging population. This will involve pharmacoepidemiological research evaluating the correlation between drug-disease interactions and clinical outcomes, alongside systematic reviews and meta-analyses across various groups, particularly community-dwelling adults and those in residential care facilities.

Multimorbidity is prevalent among hospitalized patients, and many individuals are subjected to polypharmacy due to suggestions for guidelines for chronic medical problems [36]. An analysis of 12 national recommendations in the UK revealed 32 potentially significant drug-disease interactions among medications prescribed for patients with multiple medical conditions, mostly associated with chronic renal illness [28]. Prior research has shown discrepancies among disease-specific criteria and the concomitant prescription of medications leading to drug-disease interactions in these individuals [10-13]. An Australian study revealed that one third of recently hospitalized adults with diabetes experienced treatment-related medication conflicts, including the administration of corticosteroids and antipsychotics that exacerbate hyperglycemia, as well as non-steroidal anti-inflammatory drugs that may impair renal function, particularly in cases of diabetic nephropathy [10].

In separate research of older persons prescribed an antidepressant, 87 percent had at least one comorbid illness that might lead to a treatment-related conflict. Examples include antihypertensive medicines that may elevate the danger of hypotension and falls in individuals with osteoporosis, with selective serotonin reuptake inhibitors, which are linked to diminished bone mineral density and an augmented fracture risk [33, 37-39]. Likewise, almost all community-dwelling older persons with heart failure had a comorbidity that might lead to a treatment-related dispute. Individuals with comorbid diabetes who are administered metformin face an elevated risk of lactic acidosis; those with glaucoma using a topical beta-adrenoceptor

antagonist may experience hypotension and bradycardia; and patients on tricyclic antidepressants are at heightened risk for arrhythmia and orthostatic hypotension [33, 40, 41]. Although these studies illustrate the prevalence of potential drug-disease interactions stemming from comorbidities in community settings, there is a paucity of research evaluating the correlation between drug-disease interactions and hospitalizations or mortality in hospitalized older adults, who are likely at elevated risk and present an opportunity for prescribing interventions.

This research has shown the absence of a standardized criteria for drug-disease combinations in the literature. This review included research that evaluated either individual drug-disease interactions or clusters of interactions with a similar pathophysiology, such as decreased excretion in chronic renal disease. This analysis found two studies that evaluated medications contraindicated due to renal function and one study that examined a non-dihydropyridine calcium channel blocker used in individuals with heart failure. These interactions vary from the drug-disease combinations previously observed in the outpatient context. The predominant categories of disorders associated with drug–disease interactions were cardiovascular and renal problems, aligning with findings from prior research of hospitalized patients [42]. This is expected, since cardiovascular disorders represent the most prevalent category of comorbidities among both community-dwelling and hospitalized individuals [43]. Patients undergoing anti-cancer treatment may be anticipated to have elevated rates of drug-disease interactions; however, this was not seen in the trials reviewed. For example, anthracyclines are not recommended in chronic heart failure due to the risk of cardiotoxicity, whereas immune checkpoint blockers are contraindicated in autoimmune disorders because of the potential for immunological-related side effects [44-47]. This study may not have discovered these interactions due to its focus on hospitalized patients, while the treatment of solid organ tumors mostly happens in outpatient settings. Hepatic impairment may be linked to drug-disease interactions, since it is a primary route of drug excretion; however, no research on this topic were identified.

A consensus on the concept of drug-disease interactions is essential to direct further research in this domain. A documented technique exists to define drug-disease interactions, developed by a variety of expert panel via the analysis of published data and ongoing re-evaluation [48]. A consensus-based list of clinically significant drug-disease interactions has been established by a Delphi consensus method like to that used in the formulation of the Beers or STOPP criteria [9]. Nonetheless, our analysis did not identify any studies that evaluated these interactions together, which is the approach used in the development of the Beers and STOPP criteria [27]. Nonetheless, first-generation calcium channel blockers in heart failure patients and non-steroidal anti-inflammatory medicines in chronic kidney disease represented clinically significant interactions on this list, which included the two studies reported in the review [9]. Additional study is required to ascertain if these drug-disease interactions, collectively or individually, correlate with negative health outcomes, including death, readmissions, and medication-related damage [49, 50]. Novel methodologies using data mining or machine learning may effectively detect drug-disease interactions via the use of big data. This has been conducted to forecast the relationship of pharmaceutical combinations with medication-related hospitalizations; however these methodologies may find combinations prevalent in high-risk populations rather than serious drug-disease interactions [51].

The observational research used in this review were susceptible to bias, contributing to the poor confidence of the findings. Two studies exhibited a moderate risk of bias, one had a high risk of bias, and one presented a low risk of bias. Bias resulted from insufficient correction of variables, limited statistical power, and ambiguity about individuals lost to follow-up. Ridighiero et al. evaluated particular drug-disease combinations in a high-risk population having aortic valve replacement [31]. The authors discovered that the administration of diltiazem in heart failure patients correlated with a heightened incidence of all-cause hospital stays within 30 days. Diltiazem is physiologically plausible to avoid in heart failure due to its negative inotropic effects, which may trigger exacerbations of the condition. Gigante et al. demonstrated that the administration of medications prohibited due to renal function was linked to an increased risk of all-cause death or a composite outcome of any mortality or rehospitalization [32]. Nonetheless, residual confounding may have persisted in this investigation, since adjustments were made for many comorbidities but not for demographic characteristics, degree of renal impairment, or dialysis use. This is pertinent since

age, end-stage renal disease, and dialysis use are distinct indicators of mortality in this demographic [52]. The last two investigations conducted by Bingham et al. and O'Shaughnessy et al. were insufficiently powered, perhaps accounting for the absence of a meaningful correlation, a limitation that was not addressed by a meta-analysis [34, 35].

Future high-quality studies are required to rectify the methodological limitations present in the current research, including the application of statistical tools to mitigate confounding, assuring sufficient power, and reporting on attrition rates. The typical confounders in research examining medication-related outcomes include age, sex, comorbidity load, and the quantity of drugs. Comorbidities can be evaluated by tallying the number of comorbidities from established lists, such as those by Barnett et al., the Charlson Comorbidity Index, which is derived from the Worldwide Classification of Diseases, Tenth Revision codes from hospital coding, or the Cumulative Illness Rating Scale [26, 53, 54]. The Charlson Comorbidity Index is advantageous due to its correlation with negative health outcomes, including a 10-year survival rate [55]. It is preferable to incorporate other variables, such as indicators of renal and hepatic function, since these represent the primary mechanisms of drug excretion, and both persistent kidney disease and hepatic failure correlate with increased mortality and hospital admissions.

Two of the four investigations used suitable statistical methods, such as multivariate regression, to account for confounding variables. Propensity score matching is a technique used to address disparities between groups by aligning exposed and control individuals based on various baseline characteristics [56, 57]. This is said to replicate a clinical study, referred to as target trial emulation, by ensuring that the chosen participants are appropriately matched. This strategy is particularly appropriate for large databases of regularly gathered data due to the substantial number of prospective control participants available for matching. Nonetheless, residual confounding persists as a concern, as is typical in all observational research [58]. The studies reviewed inadequately documented the number of individuals lost to follow-up. Due to the reliance on frequently obtained data, it can be challenging to ascertain the number of persons lost to follow-up, in contrast to a conventional registry. Authors must disclose the environment of the data source from which results were derived. The risk of loss to follow-up is minimal when using a universal electronic medical record, a population-based dataset, or a national death registry. Nevertheless, it may be elevated in municipalities or states where numerous electronic medical records exist, resulting in incomplete coverage of the whole area. In such instances, patients may have readmissions or fatalities in a different system that is not included in the study's data source. The studies were not consistently sufficiently powered to identify a clinically significant difference in death or readmission rates. Extensive population-based datasets should facilitate the sufficient powering of research to identify clinically significant differences in outcomes, such as death or readmissions.

Given the increasing prevalence of multimorbidity and polypharmacy globally, further research is required to ascertain if drug-disease interactions correlate with mortality and readmissions among middle-aged and older persons. No studies were found that included middle-aged persons experiencing drug-disease interactions, and this demographic has been mostly omitted from research concerning IP. Despite middle-aged people being the highest absolute number of individuals with multimorbidity in the UK [26]. This systematic review only focused on hospitalized patients, perhaps explaining the scarcity of papers about middle-aged persons who are more prone to obtain outpatient treatment. Pending the completion of future research, a further systematic review on drug-disease interactions might expand the populations to include community-dwelling adults, including both younger and middle-aged individuals, as well as those residing in care facilities.

This review and our technique have numerous limitations. The absence of a standardized criteria for drug-disease interactions may have resulted in inconsistencies in the screening and review process. This was addressed by employing two reviewers for all papers, use the Australian Medicines Handbook as a reference to detect interactions, and appointing a third reviewer to resolve disputes. However, it is conceivable that publications seen by others as drug-disease interactions may have been excluded due to the authors' interpretation or the contraindications provided in the Australian Medicines Handbook for the medicine. Secondly, due to the huge quantity of articles shown initially, pertinent articles may have been overlooked.

This was mitigated by using two writers for screening and necessitating a consensus prior to the inclusion or exclusion of an article. Third, we could not include articles in languages other than English due to the absence of local translation services necessary for screening, assessment, and result extraction. This may have resulted in the omission of papers not published in English, hence limiting the generalizability of our results to non-English speaking areas.

The studies examined exhibited methodological and clinical variability, which may restrict the generalizability of these results. Each research evaluated a distinct category or cohort of drug-disease interactions. While all research examined various combinations of pharmaceuticals and disorders, some focused on a singular drug and condition (e.g., verapamil in chronic heart failure), whilst others analyzed groups of drugs associated with a certain disease state (e.g., contraindicated medications in chronic kidney disease). This is partially due to the absence of an established definition of clinically meaningful drug-disease interactions. The discovered observational studies are susceptible to residual confounding, which may have influenced the findings and the meta-analysis. Only two of the four studies accounted for confounding variables in their analysis. Among those that adjusted for confounders, one omitted age, a usual covariate in medication-related studies. Adjusting for confounders is crucial in this domain, since both medications and the comorbidities for which they are administered may independently correlate with mortality and readmissions.

5. Conclusions

Limited studies have evaluated the correlation between drug-disease interactions in hospitalized older persons and their death and readmission rates. The detected studies were susceptible to bias due to insufficient identification and correction for confounding variables, limited statistical power to discern clinically significant changes, and ambiguity about the number of participants lost to follow-up. Recognizing these shortcomings in the research, only two of the four evaluated studies demonstrated an elevated risk of readmissions or death in hospitalized patients subjected to particular drug-disease interactions. In the three studies suitable for meta-analysis, no correlation was found between drug-disease interactions as well as readmissions in older persons.

No research adequately represented hospitalized middle-aged individuals, despite the significant prevalence of multimorbidity in this demographic. The literature is constrained by the absence of an acknowledged and standardized definition of drug-disease interactions. Additional rigorous studies are required to evaluate the sorts of drug-disease interactions linked to mortality and readmission, as well as to determine whether addressing this form of inappropriate prescribing improves patient outcomes. A published agreement list of drug-disease combinations may be used in future investigations [9]. Pending these research, next systematic reviews may investigate these connections in other groups, including adults living in the community along with those in residential facilities.

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فحص شامل للتفاعلات الدوائية والتفاعلات بين الأدوية والأمراض في حالات تعدد الأدوية: التأثيرات على نتائج التصوير التشخيصي لدى البالغين في منتصف العمر وكبار السن

الملخص

الخلفية:

أدى انتشار الأمراض المتعددة بين كبار السن إلى زيادة حالات تعدد الأدوية، مما يزيد بشكل كبير من خطر التفاعلات الدوائية (DDIs) والتفاعلات بين الأدوية والأمراض .(DDIs) يمكن لهذه التفاعلات أن تؤثر سلبًا على نتائج المرضى، لا سيما في بيئات التصوير التشخيصي.

المنهجية:

هدفت هذه المراجعة المنهجية إلى تقييم العلاقة بين التفاعلات بين الأدوية والأمراض وخطر دخول المستشفى والوفيات لدى البالغين في منتصف العمر وكبار السن. تم إجراء بحث شامل عبر عدة قواعد بيانات، بما في ذلك MEDLINE وCINAHL وEMBASE وغيرها، لتحديد الدراسات ذات الصلة المنشورة حتى عام 2023. ركزت المراجعة على الدراسات التي تناولت الوصفات غير الملائمة وتأثيراتها على نتائج صحة المرضى.

النتائج:

أظهرت النتائج وجود علاقة ملحوظة بين بعض التفاعلات بين الأدوية والأمراض وزيادة مخاطر دخول المستشفى والوفيات. على سبيل المثال، تم ربط الاستخدام المتزامن لبعض مضادات ارتفاع ضغط الدم لدى كبار السن الضعفاء بزيادة خطر حدوث آثار جانبية خطيرة. ومع ذلك، كشفت المراجعة أيضًا عن نقص في التعريفات الموحدة للتفاعلات بين الأدوية والأمراض، مما يعقد مقارنة النتائج بين الدراسات المختلفة.

الاستنتاج:

تمثل التفاعلات بين الأدوية والأمراض مصدر قلق كبير في إدارة المرضى الذين يعانون من أمراض متعددة، لا سيما في البيئات الاستشفائية. تؤكد هذه المراجعة على الحاجة الملحة لوضع معايير موحدة لتحديد هذه التفاعلات وإدارتها بفعالية. ينبغي أن تركز الأبحاث المستقبلية على تطوير تدخلات مستهدفة لتقليل المخاطر المرتبطة بتعدد الأدوية، مما يسهم في تحسين سلامة المرضى ونتائجهم في الممارسة السريرية.

الكلمات المفتاحية:

الأمراض المتعددة، تعدد الأدوية، التفاعلات بين الأدوية والأمراض، نتائج المرضى، مراجعة منهجية.