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# Assessment of Clinically Evident Drug Interactions among Inpatients: A Comprehensive Systematic Review

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**Abstract:**

**Aims:** This study aimed to investigate the prevalence of clinically apparent drug-drug interactions (DDIs) among hospitalized patients.

**Methods:** A comprehensive search of PubMed, Scopus, Embase, Web of Science, and Lilacs databases was conducted to identify articles meeting predefined inclusion criteria . The search strategy utilized controlled and uncontrolled vocabulary related to "drug interactions," "clinically relevant," and "hospital." Included were original observational studies reporting DDIs in hospitalized patients, providing data for calculating prevalence, and describing drug prescriptions or DDI adverse reaction reports in English, Portuguese, or Spanish.

**Results:** Among 5,999 initial articles, 10 met the inclusion criteria. The pooled prevalence of clinically apparent DDIs was 9.2% (95% CI 4.0–19.7). Studies reported a mean of 4.0 to 9.0 medications per patient, averaging 5.47 ± 1.77 drugs. Moderate-quality studies predominantly identified DDIs through medical records and ward visits (n = 7). Micromedex® (27.7%) and Lexi-Comp® (27.7%) were commonly used databases for DDI detection, with no studies utilizing multiple databases.

**Conclusions:** This systematic review highlights that despite reported potential DDI prevalence, fewer than one in ten patients experienced clinically apparent drug interactions. Utilizing causality tools and implementing real DDI notification systems based on actual adverse outcomes are recommended strategies to mitigate alert fatigue, enhance decision-making for DDI prevention or resolution, and ultimately improve patient safety.

## Introduction:

Medications play a pivotal role in disease prevention and the enhancement of patients' health and quality of life. However, pharmacotherapy-related issues are increasingly prevalent, affecting a significant proportion of hospitalized individuals. These issues encompass events or circumstances related to pharmacotherapy that impede the desired health outcome, including inadequate medication or dosage, adverse reactions, and drug-drug interactions (DDIs). (Lima et al., 2017)

A DDI occurs when the effect of a drug is altered due to interaction with one or more other drugs, potentially diminishing or enhancing therapeutic efficacy. Undesirable DDIs pose significant health risks, particularly in hospital settings where patients often receive multiple medications and complex pharmacotherapy, coupled with clinical instability, leading to adverse outcomes such as clinical deterioration, prolonged hospital stays, and even mortality. For instance, in a study

involving hospitalized patients, DDIs between certain drugs were linked to serious adverse events. (Costa et al., 2017)

Various databases have been developed to aid prescribers in identifying DDIs. However, these databases often generate excessive and nonspecific alerts, lacking focus on the clinical relevance and appropriate management of DDIs, leading to "alert fatigue" among prescribers, where relevant alerts are disregarded amidst a flood of notifications. (Peterson & Gustafsson, 2017)

Many studies in this field do not specifically address the prevalence of clinically evident DDIs. Prior systematic reviews on the harmful effects of DDIs in hospitalized patients predominantly focused on potential or clinically relevant DDIs, with limited exploration of clinically manifested DDIs and insufficient data to calculate their prevalence independently. Therefore, this systematic review aim to fill this gap by determining the prevalence of clinically evident DDIs among hospitalized patients. (Smedberg et al., 2016)

**Methods:**

This systematic review adhered to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement .

**Search Question:**

The research question, formulated using the PICO elements (P: hospitalized patients; I: Drug-Drug Interactions; C: not applied; O: clinically manifested DDIs), aimed to determine the prevalence of clinically manifested DDIs in hospitalized patients.

**Data Source and Search Strategy:**

A comprehensive literature search encompassing PubMed, Scopus, Embase, Web of Science, and Lilacs databases was conducted for articles published . Indexed terms from Medical Subject Headings (MeSH) and other search terms related to "drug interactions," "clinically relevant," and "hospital" were utilized. The term "clinically manifested" was initially considered but later dropped due to lack of relevance to the terminologies used in retrieved studies. Search strategies were formulated using Boolean operators (AND; OR) and adapted to each database. Full search strategies are provided in supplementary materials. Clinically manifested DDIs were defined as those with evident clinical implications, excluding theoretical interactions, even if tagged as "clinically relevant" DDIs.

**Study Selection:**

Original observational studies meeting the following criteria were included: (a) identification of DDIs using an electronic DDI database; (b) confirmation of clinically manifested DDIs through laboratory tests and/or documented signs and symptoms analyzed by specialists; (c) availability of data for calculating prevalence of clinically manifested DDIs among patients, prescriptions, or DDI adverse reaction reports; and (d) publication in English, Portuguese, or Spanish. Exclusions comprised duplicate records, studies lacking abstracts or full texts, and those focusing solely on specific diseases/pharmacotherapies or drugs. Two independent reviewers conducted study selection, resolving discrepancies through discussion or consultation with a third reviewer.

**Data Extraction:**

Information extracted included author names, publication year, country, practice setting, sample characteristics, study design, duration, methods of detecting manifested drug interactions, databases used, severity of interactions, prevalence rates of clinically manifested DDIs, terminology employed, main limitations, and methodological biases. Data extraction was independently performed by two reviewers, with discrepancies resolved through discussion.

**Quality Assessment:**

Quality assessment utilized the Newcastle-Ottawa Scale (NOS) for case-control studies and the "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" for cross-sectional and prospective studies. Two reviewers independently conducted validity assessments, with discrepancies resolved through discussion.

**Statistical Analysis:**

Two-sided confidence intervals for single proportions were calculated using Newcombe's method , prevalence of manifested DDIs according to practice setting was conducted using logit transformation and a random-effects model. Heterogeneity was assessed using the I2 value,

**Results:**

**Selection of Studies:**

A total of 5,999 studies were identified in the initial database search, with 10 studies meeting the inclusion criteria, involving 6,541 patients. The selection process and the number of articles excluded at each stage are illustrated in Fig 1. Agreement between the primary evaluators was excellent for title screening (k1 = 0.94), moderate for abstracts (k2 = 0.55), and excellent for full texts (k3 = 0.92).

**Characteristics of Studies:**

The included studies were conducted across Europe (n = 8), Asia (n = 1), and North America (n = 1), employing cross-sectional (n = 4), prospective longitudinal (n = 5), and single case-control (n = 1) designs. Sample sizes varied widely (82–3,473 patients), and studies were conducted in diverse hospital settings, including internal medicine units, emergency units, intensive care units (ICUs), and geriatric units (Table 1).

**Prevalence of Clinically Manifested DDIs:**

Individual study results indicated a wide range of prevalence for clinically manifested DDIs, from 1.2% to 64.0%. The highest prevalence was observed in an ICU study by Ray et al. (2010), while the lowest was reported in a cross-sectional study by Fokter et al. (2010) focusing on an internal medicine ward (Table 1). The encompassing 6,540 patients, revealed a pooled prevalence of clinically manifested DDIs at 9.2% (CI 95% 4.0–19.7). Clinically manifested interactions were less common among patients in emergency settings compared to those in internal medicine, while higher prevalence was noted among patients in geriatric and ICU settings (Fig 2).

**Detection of Drug Interactions:**

Detection methods for clinically manifested DDIs varied, with medical records and ward visits being the most common approach (n = 7), followed by medical records alone (n = 3). Electronic databases such as Lexi-Comp®, Micromedex®, Stocley®, and Epocrates® were utilized, with none of the studies employing more than one database. Pharmacist involvement in DDI detection varied across studies, with only three studies incorporating pharmacists into the evaluation team (Table 1).

**Assessment of Methodological Quality:**

Quality assessment revealed a good methodological quality for the case-control study and a mix of low, reasonable, and good quality among cross-sectional and prospective studies (S2 and S3 Tables).

**Fig 1. Flow diagram describing the selection process of the study.**

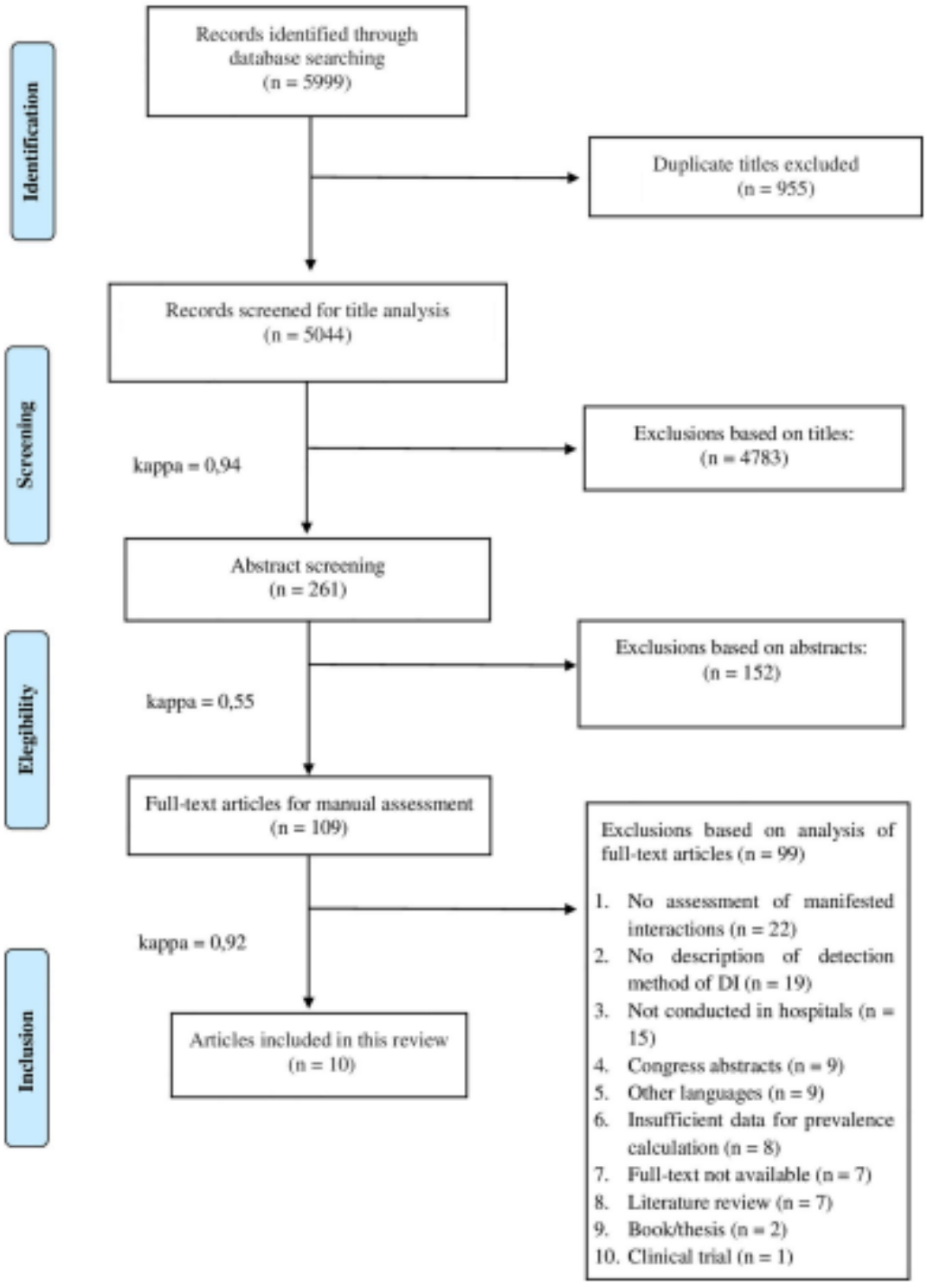

**Table 1. Characteristics of studies assessing drug interactions in hospitalized patients.**

| Author, year | Study Design | Duration | Detection Method of DI | Database | Sample Size | Number of Clinically Manifested DDIs | Main Limitations |
|---|---|---|---|---|---|---|---|
| Herr et al., 1992 | Cross-sectional | 1 month | Medical record and Ward visit | Hansten Drug Interaction Knowledge | 340 patients | 5 | NR |
| Egger et al., 2003 | Prospective longitudinal | 4 months | Medical record and Ward visit | NR | 163 patients | 26 | NR |
| Blix et al., 2008 | Multicenter prospective | 10 months | Medical record and Ward visit | Stocley1 | 827 patients | 99 | NR |
| Fokter et al., 2009 | Cross-sectional | 12 months | Medical record | Micromedex1 | 323 patients | NR | Retrospective study; Sample size |
| Ray et al., 2010 | Prospective longitudinal | 10 months | Medical record and Interview | Epocrates1 | 400 patients | 208 | NR |
| Muñoz-Torrero et al., 2010 | Case control | 2.5 months | Medical record and Ward visit | Lexi-Comp1 | 405 patients | NR | Evaluation of only pharmacokinetic DDIs; Study duration |
| Marusic et al., 2013 | Prospective longitudinal | 3 months | Medical record and Ward visit | Lexi-Comp1 | 222 patients | NR | Patient follow-up time was short; Only one database used |
| De Paepe et al., 2013 | Cross-sectional | 0.75 month | Medical record | Lexi-Comp1 | 82 patients | 18 | Study duration; Underreporting of patient history |
| Bucşa et al., 2013 | Prospective longitudinal | 3 months | Medical record and Ward visit | Micromedex1 | 305 patients | 14 | Faulty documentation and/or information; Monocentric study |
| Marino et al., 2016 | Cross-sectional | 11 months | Medical record | Micromedex1 | 3,473 patients | 464 | Faulty documentation and/or information; Monocentric study |

**Table 2. Prevalence of drug interactions in hospitalized patients.**

| Author, year | Sample | Sample Size | Average of Number of Drugs per Patient | Prevalence of Clinically Manifested DDIs [%] (95% CI) |
|---|---|---|---|---|
| Herr et al., 1992 | Patients | 340 | NR | 1.5 (0.6–3.4) |
| Egger et al., 2003 | Patients | 163 | NR | 14.7 (10.1–21.0) |
| Blix et al., 2008 | Patients | 827 | 4.8 | 8.8 (7.1–11.0) |
| Fokter et al., 2009 | Patients | 323 | 5.0 | 1.2 (0.5–3.1) |
| Ray et al., 2010 | Patients | 400 | 9.0 | 64.0 (59.2–68.6) |
| Muñoz-Torrero et al., 2010 | Patients | 405 | 5.0 | 26.4 (22.4–30.9) |
| Marusic et al., 2013 | Patients | 222 | NR | 9.5 (6.3–14.0) |
| De Paepe et al., 2013 | Patients | 82 | 5.0 | 18.3 (11.4–28.0) |
| Bucşa et al., 2013 | Patients | 305 | 4.0 | 3.6 (2.0–6.4) |
| Marino et al., 2016 | Patients | 3,473 | NR | 5.6 (4.9–6.4) |

**Table 3. The overall proportion of clinically manifested DDIs according to practice setting.**

| Setting | Number of studies | Pooled proportion of clinically manifested DDIs (95% CI) | I^2 (%) |
|---|---|---|---|
| Emergency | 3 | 5.5 (1.7–16.6) | 94.5 |
| Internal Medicine | 5 | 6.8 (2.7–16.2) | 97.1 |
| Geriatric Unit | 1 | 14.7 (10.1–21.0) | - |
| ICU | 1 | 64.0 (59.2–68.6) | - |
| Overall | 10 | 9.2 (4.0–19.7) | 99 |

**Table 4. Terminologies used in the studies included in this review.**

| Reference | Terminology used | Definition of clinically manifested DDI |
|---|---|---|
| Herr et al., 1992 | Positive drug interaction | At least one sign indicated a drug interaction |
| Egger et al., 2003 | Clinically relevant drug interaction | NR |
| Blix et al., 2008 | NR | NR |
| Fokter et al., 2009 | NR | NR |

| | | |
|---|---|---|
| Ray et al., 2010 | Adverse reaction caused by drug interaction | If drug interactions caused an adverse reaction |
| Muñoz-Torrero et al., 2010 | NR | NR |
| Marusic et al., 2013 | Actual drug–drug interactions | When a drug interaction causes an adverse drug reaction |
| De Paepe et al., 2013 | Clinically relevant drug interactions | When drug interactions caused drug withdrawal and/or dose modification |
| Bucşa et al., 2013 | Drug-drug interactions cause adverse drug reactions | A drug interaction that resulted in one or more adverse reactions |
| Marino et al., 2016 | Actual drug-drug interactions | NR |

**Discussion**

The findings reveal that despite a substantial proportion of inpatients being exposed to potential DDIs, only approximately 1/10 of hospitalized patients actually experience clinically manifested DDIs, as confirmed through laboratory testing, chart review, and/or physical examination. This suggests that strategies aimed at preventing and managing DDIs should not solely rely on potential DDI information from electronic databases. Utilizing these databases to generate alerts for the prevention of clinically manifested DDIs may overstate the problem and lead to unnecessary interventions, complicating clinical workflows and potentially causing conflicts among healthcare professionals. (Pharmaceutical Care Network Europe, 2018)

Our analysis indicates that the prevalence of clinically manifested DDIs is notably higher among ICU patients (64.0%) compared to non-ICU inpatients. This discrepancy may be attributed to factors such as the higher number of prescribed drugs and increased use of medications with narrow therapeutic indices in ICU patients, as well as a higher prevalence of patients with organ failure. Effective models for DDI prevention and management should integrate DDI warning systems with pharmacist assessments to mitigate alert fatigue associated with DDIs that may not always manifest clinically. (Basger et al., 2014)

The review also underscores the importance of thorough medical record reviews and patient interviews in detecting clinically manifested DDIs, as these methods were found to be most effective in identifying such interactions. Although databases for DDIs are commonly used by healthcare professionals, their limitations lie in their lack of clinical context and potential overestimation of the problem. Combining multiple DDI-related research programs may enhance sensitivity in identifying clinically manifested DDIs. (Mousavi & Ghanbari, 2017)

Furthermore, the assessment of DDI severity is crucial for clinical decision support, yet it was not consistently reported across studies. Future research should aim to address the severity of DDIs and their association with patient signs and symptoms. Standardization of terminologies, concepts, and methods for detecting clinically manifested DDIs is imperative for comparing prevalence rates across studies and optimizing DDI prevention, identification, and management strategies. (Lenssen et al., 2016)

While the majority of the included studies demonstrated moderate to good quality, our analysis is not without limitations. Sample size issues in some studies may affect prevalence rates, and

statistical heterogeneity was observed across studies. Additionally, potential biases in assessing the causality of clinical manifestations should be considered. (de Oliveira-Filho et al., 2017)
In conclusion, our systematic review shed light on the prevalence and characteristics of clinically manifested DDIs in hospitalized patients, emphasizing the need for comprehensive strategies to prevent, detect, and manage these interactions effectively. Further research should focus on standardizing terminology and methodology in this area to facilitate better comparison and understanding of DDI prevalence and outcomes. (Zenziper Straichman et al., 2017)

**Conclusion**

In conclusion, this systematic review underscores the importance of recognizing clinically manifested drug-drug interactions (DDIs) in hospitalized patients. Despite the widespread prevalence of potential DDIs in the literature, our findings reveal that less than one in ten patients experience clinically manifested drug interactions. Notably, patients in intensive care units (ICUs) are significantly more susceptible to these adverse events compared to non-ICU patients, highlighting the critical need for early detection and resolution, especially during periods of high ICU bed occupancy rates.
Understanding the prevalence of clinically manifested DDIs can streamline the workflow of healthcare professionals in the hospital setting, reducing alert fatigue, facilitating decision-making for DDI prevention or resolution, and ultimately enhancing patient safety.
Moving forward, prospective studies are warranted to better understand and address the clinical manifestations caused by drug interactions in hospitalized patients. Furthermore, future research should focus on identifying risk factors associated with clinically manifested DDIs, aiding clinicians and pharmacists in identifying high-risk patients and implementing preventive measures effectively.

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