Assessment of the latest prescribed drug-related problems

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Abstract. – **OBJECTIVE:** Drug-related problems (DRPs) could affect patient care and lead to deleterious manifestations, therefore, this investigation aimed to review the recently published studies concerning DRPs to improve their availability to clinical pharmacists, hoping that this information will be supportive and relevant to their practice settings.

MATERIALS AND METHODS: A search of Elsevier, Sage, Springer/Nature, and Wiley online libraries on Egyptian Knowledge Bank (EKB) was limited to the cumulative period from 1/1/2015 to 20/10/2020. The abstracts of 156 articles were critically reviewed and 50 articles were included based on relevance while excluding books. The selected articles reported DRPs and different strategies to reduce them. Moreover, drug-drug interactions (DDIs) in various patient populations were confirmed by many articles. Additionally, potential drug-drug interactions (pDDIs) predisposing factors were reported by others.

RESULTS: 24 articles (48%) illustrated DDIs, 5 articles (10%) demonstrated ADRs, 4 articles (8%) showed medication errors (MEs), and 25 articles (50%) revealed efforts to reduce DRPs. The psychiatric population is at the utmost risk of pDDIs. Polypharmacy was the furthest recurrently reported risk factor related to DDIs. Adverse drug events (ADEs) increased healthcare costs. Different strategies to avoid DRPs were published through the stated period.

CONCLUSIONS: Our findings can be supportive to healthcare professionals in enhancing their patients' quality of care by reducing the exposure to ADEs.

Key Words:
Prescription error, DRPs, DDI, MEs, Adverse reaction, Adverse effect, Prescription problem.

Introduction

Optimum patient care is the utmost preference in healthcare systems. However, the safety of patients could be negatively affected leading to possible drug-related problems (DRPs)[1]. DRPs are settings concerning drug treatment that hinder the intended rational outcomes, including supra-therapeutic doses, lower doses than recommended, and adverse drug effects (ADEs). A medication error (ME) is defined as an avoidable mishap during prescribing medications or their dispensing, as well as the inappropriate way of treatment. It varies from an ADE that is known as a non-intended and unanticipated response to a drug[2].
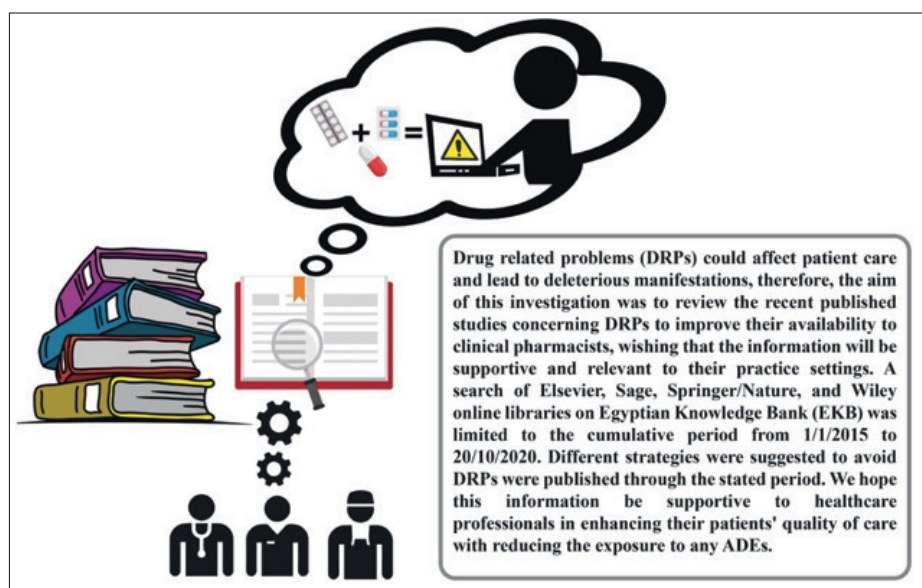
All patients, especially geriatrics, face a pronounced risk of DRPs or facing MEs as they receive more medications than any other population (polypharmacy).

These DRPs result in up to 30% of hospitalizations among geriatrics[3-5]. Regrettably, in the preceding decade, numerous approaches have failed to improve geriatrics quality of life (QoL) and minimize treatment costs; though, this population represents about 15-30% of all drug-related hospital admissions. The World Health Organization (WHO) recently reported that >50% of all medications are prescribed, dispensed, or sold improperly. Moreover, ADEs lead to >3.7% of all hospital admissions[6]. MEs are appraised to escalate hospital costs in the US by approximately $2 billion each year. Annual deaths due to MEs stay at around 7,000[2]. Likewise, a review reported that DRPs cost

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Drug related problems (DRPs) could affect patient care and lead to deleterious manifestations, therefore, the aim of this investigation was to review the recent published studies concerning DRPs to improve their availability to clinical pharmacists, wishing that the information will be supportive and relevant to their practice settings. A search of Elsevier, Sage, Springer/Nature, and Wiley online libraries on Egyptian Knowledge Bank (EKB) was limited to the cumulative period from 1/1/2015 to 20/10/2020. Different strategies were suggested to avoid DRPs were published through the stated period. We hope this information be supportive to healthcare professionals in enhancing their patients' quality of care with reducing the exposure to any ADEs.

Graphical abstract. The latest published studies regarding drug related problems (DRPs) were reviewed to enhance their accessibility to clinical pharmacists and other healthcare providers. Our findings can improve patient care by decreasing the exposure to adverse drug events (ADEs).

the Australian healthcare system US$660 million every year[1]. A questionnaire, involving 300 healthcare practitioners to survey the type and the rate of MEs, showed that 30.5% of mortalities were due to MEs[2]. Furthermore, another 18-month prospective, cross-sectional Iranian research was designed to assess the rate, nature, clinical importance, and direct-related costs of MEs in an academic nephrology ward observed by clinical pharmacists. 1373 MEs on 350 patients were detected by clinical pharmacists, meaning that 86.2% of the admitted patients suffered at least one ME. Utmost MEs (96.1%) occurred during medications prescriptions and the rest were by nurses during medicine transcription or administration[7].

Recent progress provides novel strategies for DDI prevention. In a previous study, 18 prescribers and 8 medication safety professionals were interviewed about detecting DDIs and their opinions on computerized approaches to avoid DDIs. None of the prescribers admitted total confidence in detecting serious DDIs and top prescribers thought computerized alerts as the most helpful approach for avoiding DDIs[8]. A review article on new research on MEs and adverse drug effects in the geriatric population showed that reviewing medications treatment and providing feedback to physicians enhanced the process of medication prescriptions[9]. The objective of our article is to review, summarize and emphasize the latest published studies regarding DRPs to increase their accessibility to clinical pharmacists. We hope it will be helpful and pertinent to their practice settings. In the meantime, this study would be supportive of any future review on DRPs.

Materials and Methods

Study Eligibility

The articles included in this study are peer-reviewed, full text, and limited to English journals with a specified study period. These articles illustrated reviews, and prospective, retrospective, or cross-sectional observational studies that revealed DRPs such as DDIs, ADRs, ADEs, and MEs. Also, articles demonstrating some valued efforts to diminish DRPs were included.

Search Strategy

An electronic search of Elsevier, Sage, Springer/Nature, and Wiley databases as part of the great digital library, Egyptian Knowledge Bank (EKB), was restricted to the accumulative period from 1/1/2015 to 20/10/2020. The search was conducted through 4 phases and depending on the following Queries: *prescription AND error AND missed information* for phase 1, *DDI AND prescription* for phase 2, *DDI AND (prescription) AND (error) AND (adverse reaction) OR (adverse effect)* for phase 3, *DDI AND (prescription) AND (error OR*

problem) AND (adverse reaction) OR (adverse effect) for phase 4. Phases 1, 2, and 3 were limited to the dates between 1/1/2015 to 1/6/2019. Phase 4 search was extended from 1/6/2019 to 20/10/2020. Abstracts of identified articles were reviewed for relevance. Preference was given to articles that were concerned with DRPs. Exclusion criteria included books, non-English language literature, and material irrelevant to the objectives as described in Figure 1.

Data Extraction

Data extraction was conducted by 5 researchers (MGM, MSM, ZAA, YLY, AIA, and KMZ) who separately evaluated all selected articles to extract the relevant ones for this review. The discrepancies were resolved through compromise. The inclusion process was performed by one researcher (MGM) and in case of uncertainty about article inclusion, a second researcher (MAR) was consulted.

Results

Search Results

A preliminary list consisted of collected articles (156) with 26 articles from phase 1, 30 articles from phase 2, 39 articles from phase 3, and 61 articles from phase 4. After excluding books and reviewing the abstracts of these articles for relevance, 50 articles were included with 9 articles from phase 1, 15 articles from phase 2, 9 articles from phase 3, and 17 articles from phase 4 as depicted in Figure 1. Table I shows the 50 included articles which illustrated DRPs and different strategies to reduce them. Furthermore, Table II reveals certain efforts to decrease DRPs.

DRPs

The following sections report DRPs as DDIs, ADRs, and MEs.

DDIs

DDIs are the results from a combination of at least 2 drugs that lead to change in potency, safety, or efficacy of one of them because of the other drug[10-12], which could put the patient's life at risk of hospitalization or death in case of severe drug interaction[10].

The major risk factors for DDIs include older age[10,12-26], poly-pharmacy[10,12-18,21-29], medical co-morbidity[12,13,20,22-28], genetic variability in drug pharmacokinetics[13,15,16,27-29], multiple prescribers at different locations[13,15,16], hospital stay[14,23,26],

and drug specific properties including narrow therapeutic index[13,29]. Moreover, anti-thrombotic[23], anti-coagulant[23], anti-arrhythmic[23], anti-epileptic[20,22,23], narcotic medications[15,23], as well as psychiatric medications such as antidepressant, anxiolytics, sedative, hypnotics and anti-psychotics are frequently involved in DDI[13,17,22,28,29].
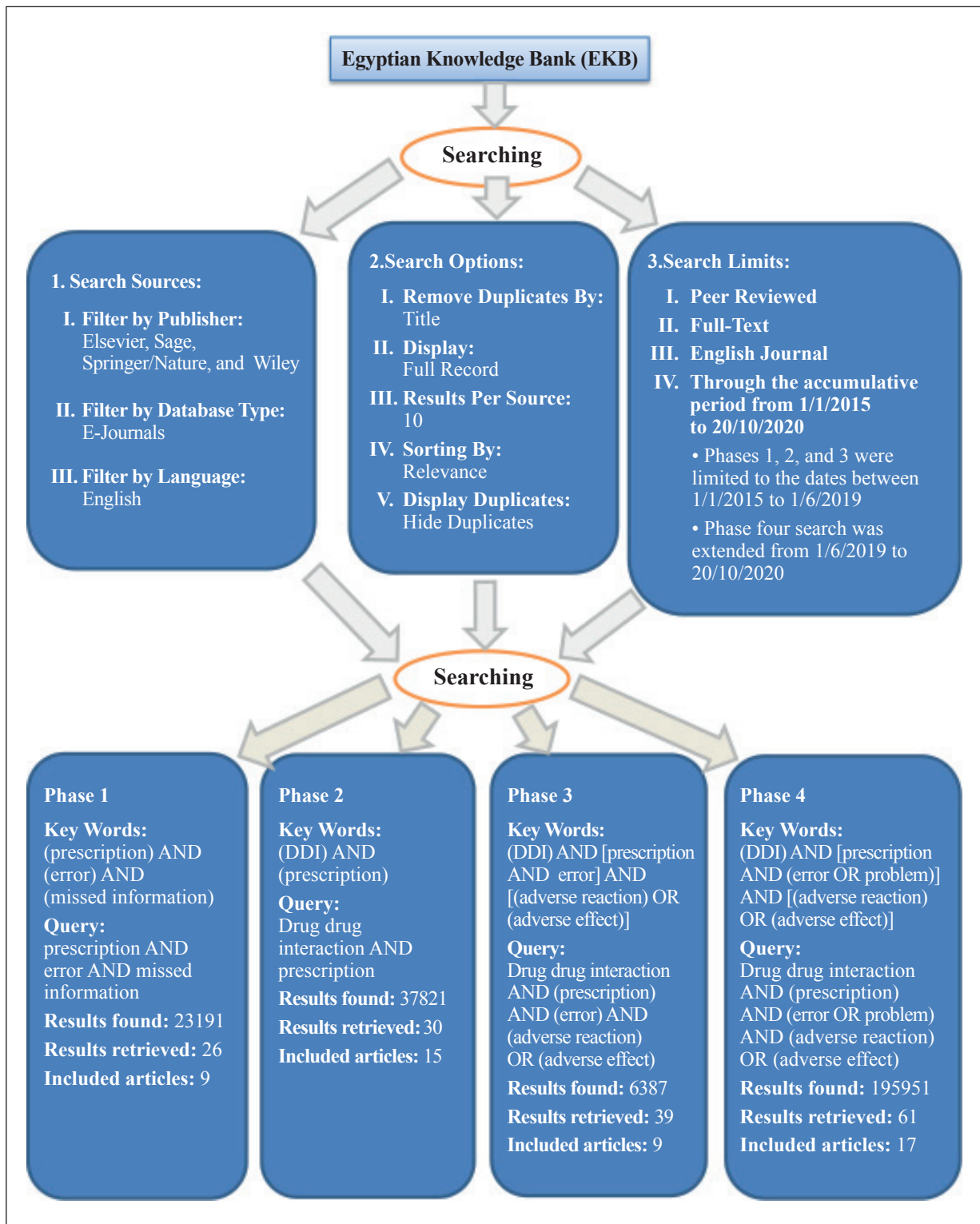
Alcoholic Patients

The US and some European countries have approved potential drug-drug interactions (pDDIs) of specific drugs used for the cure of alcohol use disorders (AUD) such as benzodiazepines, baclofen, disulfiram, and sodium oxybate. For instance, the co-administration of opiates and benzodiazepine stimulates cross-tolerance causing dependence deterioration. Also, when diazepam is taken with digoxin, urinary excretion of digoxin is decreased because diazepam elevates digoxin half-life. Moreover, baclofen and opiates combinations increase the hazard of sedation and respiratory depression. In addition, disulfiram combination with warfarin may increase the warfarin effect by chelating the metal cations essential for the production of active prothrombin. Besides, the use of disulfiram with tricyclic antidepressants (TCAs) may increase the effect of TCAs by blocking the action of cytochrome P450 2C9 (CYP2C9). Further, in the case of using sodium oxybate with lorazepam, it enhances sleepiness. When greater doses of sodium oxybate (up to nine grams per day) are taken with greater doses of hypnotics, opioids, or antidepressants, an additive effect was observed[27].

Alzheimer's Disease (AD) Patients

Prescribing several psychotropic agents with anticholinergics drugs in AD patients is the leading cause of DDIs concerning this population[17]. A French longitudinal prospective study between 5/2010 and 11/2011 reported that polypharmacy among dementia-suffering geriatrics is responsible for liberating DDIs that may develop ADRs among these patients[18].

Breast Cancer Patients

These patients are highly susceptible to pDDIs due to polypharmacy. A Pakistan study[30] recruited 150 patients at two large hospitals to identify pDDIs incidence and triggers. The study relied on Medscape mobile application and Micromedex version II. 92% of the patients suffered from pDDIs. Furthermore, DDIs severity was estimated as major in 62.2% of the patients.

Egyptian Knowledge Bank (EKB)

Searching

1. Search Sources:

I. **Filter by Publisher:**
Elsevier, Sage,
Springer/Nature, and Wiley

II. **Filter by Database Type:**
E-Journals

III. **Filter by Language:**
English

2.Search Options:

I. **Remove Duplicates By:**
Title

II. **Display:**
Full Record

III. **Results Per Source:**
10

IV. **Sorting By:**
Relevance

V. **Display Duplicates:**
Hide Duplicates

3.Search Limits:

I. **Peer Reviewed**

II. **Full-Text**

III. **English Journal**

IV. **Through the accumulative period from 1/1/2015 to 20/10/2020**
• Phases 1, 2, and 3 were limited to the dates between 1/1/2015 to 1/6/2019
• Phase four search was extended from 1/6/2019 to 20/10/2020

Searching

Phase 1

Key Words:
(prescription) AND (error) AND (missed information)

Query:
prescription AND error AND missed information

Results found: 23191

Results retrieved: 26

Included articles: 9

Phase 2

Key Words:
(DDI) AND (prescription)

Query:
Drug drug interaction AND prescription

Results found: 37821

Results retrieved: 30

Included articles: 15

Phase 3

Key Words:
(DDI) AND [prescription AND error] AND [(adverse reaction) OR (adverse effect)]

Query:
Drug drug interaction AND (prescription) AND (error) AND (adverse reaction) OR (adverse effect)

Results found: 6387

Results retrieved: 39

Included articles: 9

Phase 4

Key Words:
(DDI) AND [prescription AND (error OR problem)] AND [(adverse reaction) OR (adverse effect)]

Query:
Drug drug interaction AND (prescription) AND (error OR problem) AND (adverse reaction) OR (adverse effect)

Results found: 195951

Results retrieved: 61

Included articles: 17

Figure 1. This flow diagram shows the selection of eligible articles through period from 1/1/2015 to 20/10/2020, from Elsevier, Sage, Springer/Nature, and Wiley databases as part of the Egyptian Knowledge Bank (EKB). The search was conducted through 4 phases and depending on specific Queries. All abstracts were reviewed, and then preference was given to articles that were concerned with Drug-related problems (DRPs). A preliminary list consisted of collected 156 articles. After excluding books, non-English language literature, and evaluating the abstracts of these articles for relevance, 50 articles were included.

Cardiac Patients

DDI incidences are highly apparent in cardiac patients[14,20,22,26]. The most common DDI is that between Aspirin and clopidogrel which may cause bleeding. To identify risk factors for DDIs in Abbottabad, Pakistan, the results of 2342 hospitalized cardiac patients with an average age of 62 years, average hospitalization of 6 days, the average number of medications of 8, and most patients suffering from myocardial infarction followed by acute coronary syndrome and coronary artery disease were as follows: 5109 drug interactions classified according to severity into 2021 major pDDIs (death or serious complication), and 1979 moderate pDDIs (harmful effect and the drug should be changed). Thus, most patients have at least 2 pDDIs, one major and one moderate[14].

Special attention is needed for DDIs in cardiac patients[14,20,22] due to disease complications and therapeutic regimens[14]. Another study concluded that the complexity of pharmacological treatment developed pDDIs in such patients. Pharmacodynamic DDIs were the utmost recurring mechanism for DDIs[26].

Diabetic Patients

Certain pDDIs together and particular hypoglycemics could harm the kidney. For instance, metformin, linagliptin, and pioglitazone have negative confounding roles in causing renal insufficiency. Conversely, insulin, glipizide, sitagliptin, glimepiride, glyburide, and acarbose have positive confounding roles. The study illustrated that combining insulin with certain kidney-destructing drugs such as trimethoprim-sulfamethoxazole and ciprofloxacin has inverted its effect suggesting a possible DDI[31].

Elderly Cancer Patients

DRPs are predominant in this population. In a retrospective French multi-center cross-sectional one-year study of 106 patients, polypharmacy, of at least six medications, was found in 60.4% of the patients. DDIs appeared in 16% of them which were due to anti-cancer treatments in 47% of the total DIs. Barring chemotherapy, the medication classes involved in DRPs were psychotropic, vasodilator, analgesic, antidepressant, and lipid-lowering agents. Contraindicated drugs were found in 13.2% of patients who suffered from diabetes or cardiovascular comorbidities[21].

Endometriosis and Uterine Fibroids

The antigonadotropin elagolix, used for menstrual bleeding related to uterine fibroids and en-dometriosis-associated pain, was studied in 144 women to evaluate clinically significant pharmacokinetics' DDIs. Elagolix and ketoconazole DDI increased the elagolix plasma level by about twofold. This antigonadotropin reduced midazolam and rosuvastatin plasma level by 54% and 40%, respectively. Besides, it increased digoxin plasma levels by 32%[32].

Epileptic Patients

Epilepsy patients are at risk of DDIs[20,22] as they may suffer from enzyme induction or inhibition, alteration in protein binding, and expression of transporter protein especially in geriatrics having comorbidities requiring long-term therapy. A Polish study analyzed DDIs using IBM-Micromedex checker in 633 patients with epilepsy using questionnaires related to co-morbidities and medications used chronically. It was found that 11.7% of DDIs were major while 18.4% of them were moderate interactions. The most prevalent major interactions included ethinylestradiol/estradiol with valproate/oxcarbazepine/carbamezpines, sertraline with carbamazepine, simvastatin with carbamazepine, and olanzapine with carbamazepine[20]. Another study involved the old population using a Finnish academic hospital database (2000-2013) and the Social Insurance Institution of Finland data in 2012. The analysis covered only the DDIs between chronically used drugs and carbamazepine, oxcarbazepine, or valproic acid. Carbamazepine in 32% of its users developed a single type C (DDI that can be controlled) or D (medications co-administration should be avoided) interaction and at least 2 or more type C or D interactions in 31% of hospitalized patients. Regarding valproate, 2% of hospitalized patients suffered a class-C DDI. On the other hand, none of the patients who started oxcarbazepine treatment had type C or D DDI. Also, the first-generation antiepileptic drugs (AEDs) induced liver enzymes. In addition, they decreased plasma levels of immunosuppressants, anti-neoplastic medications, anticoagulants, cardiovascular diseases drugs, and AEDs. Accordingly, they could decrease the therapeutic efficacy of these treatments[22].

Human Immunodeficiency Virus (HIV)-Infected Geriatrics

As per various clinical trials, the DDIs rate is high in HIV-infected elderly subjects whose age was 50 plus. Antiretroviral (ARV) drugs are highly associated with pDDIs[24]. An article illus-

Table I. Selected 50 references with their main objectives.

S.	Author(s)	Main objective(s)
1	Mussina AZ, et al[10] 2019	Detect common PDDIs and estimate the influence of education on pharmacotherapy.
2	Jawaro T, et al[11] 2019	Detect frequently occurring PDDIs in patients discharged from an urban tertiary care ED.
3	Lohasz C, et al[12] 2020	Detect and predict metabolism related DDIs.
4	Monteith S, Glenn T[13] 2019	Compare the severity level of PDDIs of 6 DDIs database programs.
5	Murtaza G, et al[14] 2016	Detect prevalent PDDIs in cardiac patients to identify the incidence and sorts of PDDIs.
6	Getachew H, et al[15] 2016	Define incidence of PDDIs, degree of severity, and factors that could increase their rate.
7	Jazbar J, et al[16] 2018	Assess the incidence and factors that could increase PDDIs rate in Slovenian outpatients.
8	Kanagaratnam L, et al[17] 2016	Detect ADRs in geriatrics with cognitive disorders, "ADRprone" medicines, risk factors.
9	Kanagaratnam L, et al[18] 2017	Detect factors that increase ADRs rate in elderly patients with dementia.
10	Alrabiah Z, et al[19] 2019	Assess awareness of frequent PDDIs between community pharmacists in KSA.
11	Bosak M, et al[20] 2019	Investigate pharmacotherapy and evaluate pDDIs of AEDs in epilepsy patients.
12	Rougé Bugat M-E, et al[21] 2017	Study risk factors that affect anticancer treatment like: PIP, polypharmacy, and PDDIs.
13	Bruun E, et al[22] 2017	Investigate the rate of PDDIs in Finnish geriatrics suffering epilepsy, and co-morbidities.
14	Janković SM, et al[23] 2018	Detect risk factors linked to the occurrence of different types of PDDIs in ICU patients.
15	Livio F, Marzolini C[24] 2019	Illustrate possible prescriptions errors and risk factors for DDIs in HIV patients.
16	Ruellan A, et al[25] 2020	Demonstrate definite DDIs among antiretroviral drugs and co-administered medications.
17	Diksis N, et al[26] 2019	Determine the type, incidence, features of pDDIs in cardiovascular patients.
18	Guerzoni S, et al[27] 2018	Summarize DDIs stated in literature of the pharmacotherapy approved for AUDs.
19	AlRuthia Y, et al[28] 2019	Assess pharmacists' professional role in the observation and management of PDDIs.
20	Lai L. L, et al[29] 2019	Evaluate pDDIs in outpatient pediatrics with depression.
21	Bibi R, et al[30] 2020	Illustrate DDIs rate, clinical importance, severity, and predisposing factors in patients.
22	Davazdahemami B, Delen D[31] 2019	Examine if the order of "ADRprone" medications could elevate the risk of ADRs.
23	Polepally A, et al[32] 2020	To demonstrate DDIs between elagolix and certain drugs.
24	Fernandes FM, et al[33] 2019	Assess association between DDIs and prolongation of QT-interval in ICU patients.
25	Nguyen T, et al[34] 2020	Demonstrating ADRs arising from specific pDDIs.
26	Ferner R, Pucci M[35] 2020	To classify, detect and diagnose ADRs.
27	Lavan AH, Gallagher P[36] 2015	Outline an applied clinical approach to detect and decrease ADRs risks in geriatrics.
28	Lee C, Chen Y[37] 2019	Predisposing factors for ADRs.
29	Fernández Regueiro R, et al[38] 2019	Find if a notification software of PIP in hospitalized geriatrics can decrease ordering.
30	Jatau AI, et al[39] 2019	Create and validate an approach for a better understanding of ED visits due to ADEs.
31	Alharbi W, et al[40] 2019	Detect risk factors for MEs from the viewpoint of healthcare providers.
32	Darbishire PL, et al[41] 2019	Analyze the data on errors and appraise medication safety.
33	Lalande J, et al[42] 2018	Estimate the MEs in pediatrics in ED at a hospital as well as the causes of these MEs.
34	Santesteban E, et al[43] 2015	Assess categories and rate of MEs in neonates in ICU and evaluate the efficacy.
35	Rathish D, et al[44] 2016	Evaluate prescription dispensing in the rural region for PDDIs, errors, and medication use.
36	Joseph B, et al[45] 2019	To assess the incidence of ADRs and DDIs.
37	Peixoto de Miranda ÉJF, et al[46] 2020	To evaluate DDIs of antineoplastic and supportive care drugs with anticoagulants.
38	Horn J, et al[47] 2019	To evaluate DDIs specific alert systems in reducing DDIs notifications.
39	Toivo TM, et al[48] 2016	Use of the first Finnish online DDIs surveillance system by community pharmacists.
40	Solomon J, et al[49] 2018	Evaluate the incidence of DRPs among patients treated with oral chemotherapeutic agents.
41	Zolnoori M, et al[50] 2018	Detect ADEs and ADRs.
42	Schwartzberg D, et al[51] 2015	Estimate effect of implementing CPOE on decreasing total number and severity of OEs.
43	Kim SJ, et al[52] 2018	Estimate impact of the DUR approach to enhance patient safety.
44	Slight S, et al[53] 2018	Demonstrate the influence of the electronic prescribing system in reducing MEs.
45	Kenawy AS, Kett V[54] 2019	Evaluate the influence of automated prescription on the rates and types of MEs.
46	Garner SS, et al[55] 2015	Estimate the efficacy of an ICOS-DS in avoiding DRPs in neonates suffering LOS.
47	Venkataraman A, et al[56] 2016	Assess the influence of an automated infusion calculator on infusion rate errors.
48	Davazdahemami B, Delen D[57] 2019	Assess the role of hypoglycemics in causing acute kidney injury in Type II diabetic patients.
49	Bannan DF, et al[58] 2019	Utilize the COM-B approach to demonstrate senior health care professionals' behaviors.
50	Wang X, et al[59] 2019	Identify doubted DDIs alerts.

(PDDIs): potential drug-drug interactions, (DDIs): drug-drug interactions, (FDA): Food and Drug Administration, (ADRs): Adverse Drug Reactions, (ADEs): adverse drug events, (CPOE): Computer physician order entry, (OEs): medication order errors, (EHR): electronic health record, (NHIS): National Health Insurance Services, (DUR): drug utilization review, (LOS): late-onset sepsis, (ICOS-DS) interactive computerized order set with decision support, (DRPs): drug-related problems, (ADL): Activities of Daily Living, (ED): emergency department, (MEs): medication errors, (US): United States, (COM-B): capability, opportunity, motivation – behavior, (PEs): prescribing errors, (PIP): Potentially inappropriate prescription, (QT): QT interval on an electrocardiogram, (ICU): intensive care unit, (AEDs): antiepileptic drugs, (AUDs): alcohol use disorders.

Table II. Efforts to reduce drug related problems (DRPs) were revealed by the following articles.

Electronic DDIs resources	Pharmacist training	Pharmacist intervention	Automated systems	Patient education	Miscellaneous[¶]
Mussina AZ, et al[10] **2019**	Mussina AZ, et al[10] 2019	AlRuthia Y, et al[28] 2019	AlRuthia Y, et al[28] 2019	Solomon J, et al[49] 2018	Davazdahemami B, Delen D[57] 2019
Jawaro T, et al[11] **2019**	Alrabiah Z, et al[19] 2019	Toivo TM, et al[48] 2016	Toivo TM, et al[48] 2016	Zolnoori M, et al[50] 2018	Bannan DF, et al[58] 2019
Monteith S, Glenn T[13] **2019**		Solomon J, et al[49] 2018	Zolnoori M, et al[50] 2018		Wang X, et al[59] 2019
Jazbar J, et al[16] **2018**			Schwartzberg D, et al[51] 2015		
Alrabiah Z, et al[19] **2019**			Kim SJ, et al[52] 2018		
Janković SM, et al[23] **2018**			Slight S, et al[53] 2019		
Ruellan A, et al[25] **2020**			Kenawy AS, Kett V[54] 2019		
Diksis N, et al[26] **2019**			Garner SS, et al[55] 2015		
AlRuthia Y, et al[28] **2019**			Venkataraman A, et al[56] 2016		
Rathish D, et al[44] **2016**					
Joseph B, et al[45] **2019**					
Peixoto de Miranda ÉJF, et al[46] **2020**					
Horn J, et al[47] **2019**					
Toivo TM, et al[48] **2016**					
Total: 14 articles **Percentage: 28%**	**Total: 2 articles** **Percentage: 4%**	**Total: 3 articles** **Percentage: 6%**	**Total: 9 articles** **Percentage: 18%**	**Total: 2 articles** **Percentage: 4%**	**Total: 3 articles** **Percentage: 6%**

[¶]Miscellaneous efforts to reduce DRPs; Bannan DF, et al[58] 2019; Prescribing behaviors. Davazdahemami B, Delen D[57] 2019; The sequence of medication prescription and administration. Wang X, et al[59] 2019; A new statistical approach to detect ADEs.

trated DDIs between anti-cancer pro-drugs like ifosfamide or cyclophosphamide with ritonavir (ARV drug). The ritonavir drug hinders liver metabolism of the pro-drugs and reduces their effectiveness[12]. Important to note that new ARVs, like the inhibitors of non-nucleoside reverse transcriptase and integrase enzymes, are linked to fewer DDIs[24].

Intensive Care Unit (ICU) Patients

In critically ill patients, prolonged hospitalization and the use of ICU medications increase the risk of DDIs that may potentiate the risk of QT-interval prolongation and death. An observational cross-sectional study, conducted at the ICU of a Brazilian academic institution from May 2014 to July 2016, classified DDIs associated with QT interval abnormality into pharmacokinetics DDIs (PK-DDIQT) and pharmacodynamics DDIs (PD-DDIQT). DDIs, found in the medication profile of 283 patients, were checked by Micromedex and Lexi-interact databases. The research concluded that major interactions were due to pharmacodynamics[33].

Pediatric Population

DDIs may result in hazardous adverse events with high incidence in children. Pediatrics are more susceptible to drug interventions, especially hospitalized children. DRPs are highly associated with polypharmacy and age. A trial between March to May 2014 in the pediatric department of an Ethiopian academic hospital revealed that 176 subjects from the total 384 (45.8%) suffered at least 1 DDI. The majority of DDIs were moderate (51%), then minor (39%), and major (10%). Regarding major DDIs, the furthermost frequent interacting drugs were furosemide with gentamicin (ototoxicity and nephrotoxicity), methotrexate with co-trimoxazole (cytopenia, mucositis, hepatotoxicity, and gastrointestinal symptoms) and artemether with phenytoin (loss of antimalarial efficacy)[15]. Similarly, another study showed that 1.28 million pediatric patients had depression from 2010 to 2014 in the American outpatient care settings. In this population who suffered major depression and received pharmacotherapy, 25% had a major or moderate pDDI. Also, serotonergic

antidepressants yielded a higher rate of DDIs than other antidepressants in pediatrics[29].

Psychiatric Patients

Psychiatric patients suffer from pDDIs which are magnified by additional hazardous group characteristics like comorbidities needing treatment for multiple conditions[28]. Antipsychotics are highly associated with drug interactions[13,17,22], particularly risperidone and quetiapine that develop significant class-D interaction when given with carbamazepine[22]. Fluoxetine interaction with risperidone had strong evidence from 4 pharmacokinetic studies that illustrated a significant increase in risperidone plasma concentrations. This DDI could lengthen the QT- interval. DDIs among psychotropic medications could develop serotonin syndrome, long QT syndrome, and/or alteration in the activity of the normal nervous system[34].

ADRs

In Europe, ADRs induced hospitalizations vary from 0.5% to 12.8% of total admissions[35]. ADRs could occur due to age, physiological state, renal function, polypharmacy, inappropriate prescribing mediations, sex, and genetic predisposition[35-37]. For illustration, Benzodiazepines' lipophilicity makes it of higher distribution volume in geriatrics. Consequently, this prolongs elimination half-life and leads to drug accumulation and toxicity. Additionally, regarding renally eliminated drugs such as metformin, the glomerular filtration rate should be evaluated particularly if the acute renal illness is detected. Certain medications may require renal adjustment or stopping accordingly to minimize the risk of ADRs. Older age contributes to ADR through polypharmacy. Geriatrics are the primary sufferers of chronic diseases that necessitate many drugs to be used daily. This increases ADRs frequency through drug-disease interactions and DDIs. Gender may also play a role, as the hormonal difference may influence drug dynamics and kinetics[36]. ADEs escalate the mortality rate among the elderly due to noncompliance, dose duplication, and drug interactions. For the elderly, the problem is more complicated as 95% of them are at risk of potentially inappropriate prescriptions (PIPs) due to polypharmacy. Beers and STOPP/START criteria are the frequently used tools to improve the quality of prescriptions and the use of drugs among geriatrics. A one-year trial detected the ramifications of using a program to notify about PIPs among hospitalized geriatrics at an academic institution. Beers (2012 update)

and STOPP-START criteria (2008 version) were employed to detect PIP. Eighteen percent of the total prescriptions for the participants contained inappropriate medications. Benzodiazepines, digoxin, and spironolactone were the main contributors. Thirty-two ADEs were detected, 29 of them were related to PIPs. The five major ADEs were due to inappropriate drug combinations of lorazepam-alprazolam, haloperidol-lorazepam, haloperidol-bromazepam, haloperidol-risperidone, and alprazolam-clobazam-zolpidem[38]. Another study reported that ADEs could elevate ED admissions and healthcare costs. To illustrate factors associated with ED visits due to ADEs, a literature review covered databases Embase and PubMed between 1/2000 to 3/2018. The results outlined risk factors in hospitals in Taiwan, Spain, the US, and India as age older than 65 and the number of medications in use. In Italy, men were more prone to ADEs than women. In India and Cape Town, South Africa, diabetes and frequent doctor visits were ADEs risk factors[39].

MEs

The causes of MEs differ throughout the world. In France, about 91% of MEs related to prescription errors (PEs), while in the US 41% of MEs were due to administration errors and about 38% were due to dispensing errors. Also, MEs may differ within the same institution[40]. A study was conducted by students at an American College of Pharmacy to record MEs in community pharmacies in the US. Fifty-one percent of the students reported 1 to 10 MEs and 30% of them recorded 11 to 30 MEs. The detected errors were wrong directions (34%), wrong drug (14%), wrong drug strength (13%), or wrong patient (12%)[41]. Furthermore, MEs detected in pediatrics occur due to their unique physiological features and their lower tolerance to errors. A study evaluated MEs in a pediatric ED at a French academic hospital. 11,573 hand-written prescriptions were analyzed for children below 15 years. The rate of MEs was only 0.9%. Mainly, these errors were associated with analgesics (51%) and antibiotics (30%). The analgesics involved were acetaminophen (26.5%), ibuprofen (10.8%), and codeine (9.8%). Amoxicillin, an antibiotic, was frequently involved in MEs. Most errors were due to lack of knowledge (57.8%) or calculation slips (21.6%). MEs were committed by trainees (58.8%), senior staff members (29.4%) and nurses (11.8%)[42]. Neonates are highly vulnerable to ME hazards due to liver immaturity and limited kidney capacities which result in challenging issues. Also,

90% of the drugs used in neonates are either unlicensed drugs or off-label[43].

Efforts to Reduce DRPs

To assess the factors for pDDIs and their rate in outpatient settings, a Slovenian study used Lexi-Interact Module and involved 1,179,803 subjects. The study showed that 9.3% of the Slovenians are at risk of type D and X pDDIs which were observed amongst the elderly and females. Further, the study revealed that both aging and polypharmacy were associated with clinically significant pDDIs linked to anticholinergic adverse effects, bleeding, cardiovascular deteriorations, or nervous system inhibition[16]. Similarly, a Sri Lankan study on 1000 prescriptions investigated pDDIs using Medscape online DI checker. The author claimed that about 53% of the whole prescriptions showed pDDIs. The maximum number of pDDIs/prescription was 21 in contrast to 33 in India[44]. Since pediatrics are extremely prone to DRPs, thoroughgoing monitoring could improve clinical outcomes. Another study considered DRPs in 176 pediatric patients in an Indian oncology department using the Lexi-interact database and showed that 67% of the patients had ADRS. A rash is regarded as the utmost repeated ADR. Besides, vincristine was the most common cytotoxic agent that developed ADRs. Among the whole, 74.5% of the ADRs were avoidable with 57.6% of them being moderate. Regarding DDIs, 38.13% of the prescriptions necessitated monitoring. The majority of DDIs were avoidable and moderate with only 10 classified as category X[45]. Also, cardiac patients are at serious risk of pDDIs. A study evaluated the rate of pDDIs in 200 cardiac patients at an Ethiopian hospital. The overall prevalence of pDDIs in 673 prescriptions was 74.41%. Nearly one-third of DDIs were classified as major and about 45% were moderate[26]. To reveal the reasons for pDDIs in ICU patients, a Serbian study used 3 DDIs checkers: Medscape, Epocrates, and Micromedex. Results showed a high percentage of pDDIs were detected by Medscape followed by Epocrates and then Micromedex. A high rate of DDIs was associated with antiarrhythmic medications, anticonvulsants, male sex, length of hospitalization, surgery, polypharmacy, physicians' knowledge, attitudes, and behaviors. The most frequently occurring DDI (41.3%) was between midazolam and tramadol which depresses the nervous system[23]. Comparatively, DDIs between supportive care and anticancer medications with anticoagulants could lead to severe DRPs.

Another study reviewed literature and assessed the deviation among several DDIs databases. By reviewing data of 7 DDIs databases, 264 summaries of products characteristics, and more than 50 case reports and case series that assessed regimens containing chemotherapy and anticoagulants, the results revealed the following: DDIs between 257 anticancer and supportive care medications with anticoagulants illustrated 1799 associations, 10.2% were clinically significant DDIs, and 2% were contraindicated. Warfarin showed the highest DDI tendency among the other investigated anticoagulants. Enoxaparin and fondaparinux had very few DDIs[46]. Analogously, DDIs are arising upon discharge from hospitals, particularly from ED. Depending on Lexicomp DDIs checker, a study was concerned with the most common DDIs after discharge to check them and educate patients regarding the need for ADE monitoring. A total of 858 prescriptions were written upon the discharge of 500 patients. Half of the prescriptions included DDIs. Among them, 1.6% were classified as category X, 22% as category D, 60% as category C, and 15.6% as category B. The top drugs involved in the detected DDIs were oxycodone, ciprofloxacin, prednisone, acetaminophen, ibuprofen, and albuterol. The analysis showed that myoclonus was developed after 7 days of treatment with ciprofloxacin and oxycodone in an 80-year-old female. As well, oxycodone/acetaminophen combination with diazepam or cyclobenzaprine could increase the risk of death. Further, Lisinopril and ibuprofen interaction increased the rate of acute renal failure (ARF)[11]. Clinicians should be aware that different DDI checkers could detect the same DDIs, however, the DDI categories will not share the same definitions. Consequently, more than one program should be checked for increased accuracy[13,23].

Another study analyzed DDIs among 100 drug pairs using 3 subscription drug interaction database programs (Clinical Pharmacology, Lexicomp, and Micromedex) and 3 open-access programs (Drugs.com, Medscape, and Epocrates). For each drug pair, if the class of a probable DDI was the same in the entire 6 database programs, the agreement percentage is 100%, in case of only 5 of the 6 databases classifications were the same, it is 83%, 67% for 4 of 6, 50% for 3 of 6, and 33% for 2 of 6. It was found that the overall agreement percentage is 66%[13]. Likewise, to detect pDDIs between ARVs and other medications used in geriatrics and to evaluate DDIs classifications among 3 DDIs databases, pharmacological treatment of 239 HIV-infected

elderly patients was evaluated in 6 French institutions. The subjects who suffered at a minimum of one DDI were 25.1% where 126 DDIs were detected in this population. Twenty-three DDIs were observed in 17 patients and classified as major DDIs. Only 7 of them were detected in the 3 databases concurrently used[25].

Similarly, patient-related DDIs notification is a helpful model to decrease the sum of DDIs notifications to increase the suitability of notifications and decline the probability of notification fatigue. A medical center studied an embedded system with several clinical aspects including interaction checking capability but, the problem was that notifications for major DDIs were not all the time a real DRP that necessitated a clinical action. Hence, a study developed patient-related algorithm-based DDIs notifications for 7 of the frequent DDIs pairs found over a 30-day trial at the center. The system generated normally an average of 185.3 notifications for each drug pair throughout the study period before the intervention. After applying the algorithms, the reduction in the individual notification ranged from 11.3% to 93.5% resulting in a reliable notification system without neglecting important alerts[47].

To assess the impact of educational campaigns on emergency hospitals in Aktobe and Uralsk cities of Kazakhstan, the prevalence of DDIs was evaluated using electronic DDI resources. The campaigns decreased major DDIs by 18.2% in patients with cardiovascular disorders at Aktobe city hospital (Kazakhstan) compared to the hospital of Uralsk (Kazakhstan)[10]. In another study, a self-administered questionnaire was made to evaluate DDIs at 283 community pharmacies in Saudi Arabia. The study highlighted 26 pairs of medications found to be the most prevalent DDIs. From the overall medication pairs, only 5 DDIs were recognized properly by almost all pharmacists necessitating tools like electronic DDIs checkers. Besides, continuous education was found to be highly valuable[19]. A low level of pharmacists' interventions towards risks such as polypharmacy, comorbidities, and old age increases the probability of DRPs. To reveal how pharmacists could manage DDIs threats in outpatient care, a study used electronic medical records of 270 psychiatric outpatients at a Saudi Arabian hospital. DDIs and pharmacists' interventions were recorded using an implemented automated system. Both major and moderate DDIs stood at 213. Pharmacists made interventions in 5.6% of them, particularly in the case of polypharmacy, old age, severe DDIs, and the prescription of anticoagulants and/or lithium[28]. Similarly, another study explained that community

pharmacists could manage DDIs risks in outpatient settings in Finland[48].

Moreover, education of patients by pharmacists could decrease DDIs and ADEs. A study analyzed the DRPs among 100 cancer outpatients at an American hospital. The study showed that 79% of patients were reported chemotherapy-induced toxicities and 55% of these toxicities were categorized as severe and led to hospitalization in 19% of the patients. Besides, pDDIs occurred in 55% of patients and only 27% of the patients were educated by pharmacists. Consequently, the study interpreted that pharmacist could educate patients, and prevent and manage DRPs[49]. Moreover, to obtain data about DRPs and medication efficacy, a study extracted information from a health-care forum called "askapatient.com" for patients who have used serotonergic antidepressants. The data were classified into several classes including ADRs, withdrawal symptoms, DDIs, and drugs ineffectiveness. This has eased the identification of ADRs from patients' previews and experiences[50].

For healthcare services, the American medicine institute recommended the application of patients' electronic medical records (EMRs) and automated physician order entry[51]. The drug utilization review (DUR) system in South Korea was tasked to review drug prescriptions and detect any prospective ADE. With 154,585 outpatients and conditions that mimic ADEs, the introduction of this system decreased average dose prescribed from 1.11 to 1.07 times the defined daily dose (DDD). Also, DDIs decreased by 3.6% and ADEs in geriatrics decreased by 9.6%[52]. Analogously, an English observational study at an educational institution included 3,824 patients to check the prevalence of MEs per hospital admission. The study evaluated the kind and rate of MEs after optimization of automated prescriptions. Dose, medicine-reconciliation, and unnecessary treatment delay MEs were the most frequent kinds of MEs. Medication dose errors declined with time through the study[53]. Similarly, a study evaluated an automated system for MEs in an Egyptian hospital where electronic prescriptions reduced dispensing errors by 1.2% and increased the prescriptions proportion which was devoid of errors by 18.2%[54]. Comparably, an American study in a neonatal ICU evaluated an electronic system that assisted clinical decisions. The system showed a warning message if the selected antibiotic did not counterpart the decision support. The total level of errors declined significantly[55]. An English study demonstrated the reduction of MEs to < 1% from 32.6%[56] using an electronic system combining automatic prescribing and physician order entry.

The sequence of medication prescription and administration could increase DRPs, particularly ADRs. A sequential pattern mining approach to 377,000 diabetic patients' electronic health records was applied. The findings provided evidence for the probable influence of medication sequence on DRPs occurrence proved by the detection of certain sequential patterns that happened more recurrently in specific patients than others[57].

In addition, studies showed PEs still persevere due to prescribing behaviors. Accordingly, a study was conducted in a department of pediatrics oncology at a Saudi Arabian hospital to explore senior doctors' behaviors using "COM-B" approach. It investigated capability (C), opportunity (O), and motivation (M) - behaviors (B). The study highlighted behaviors linked to physicians' capabilities such as lack of knowledge and inappropriate usage of electronic programs. The behaviors associated with opportunities involved heavy duties and insufficient access to patients' data. Further, the physicians' behaviors related to motivation include following recommendations without questioning and poor communication[58].

Furthermore, ADEs due to DDIs are discovered mostly in the post-marketing phase. Premarketing clinical trials focus only on the investigated medications' side effects and efficacy. Post-marketing ADEs are detected by a spontaneous reporting system (SRS). Although SRS is valuable for a healthcare provider, it is limited by false-positive rates and bias. Consequently, a new statistical approach can be used as an accompaniment to the existing system. This approach is called the "propensity score-adjusted three-component mixture model (PS-3CMM)". It can evaluate false rates and eliminate bias for ADEs reports[59]. Efforts to reduce drug related problems (DRPs) were summarized in Table II.

Clinicians' Role in Preventing DRPs Together with Pharmacists

Clinicians need expertise in medication technologies to stop DRPs[58]. More than one DDIs-software can ensure correct treatment recommendations[13,23]. Modern technologies have reduced DRPs through prescribing and dispensing phases[54]. Also, physicians need sufficient knowledge to recommend pharmacological treatments properly[58]. Also, clinical pharmacists should educate patients, evaluate adherence, and handle ADRs[49].

Discussion

This article revealed that definite populations needed close follow up for DRPs such as cardi-ac patients[14,20,22,26], psychiatric patients[13,17,22,28,34] specially, pediatrics suffering depression[29], ICU patients[33], and geriatrics[10,12-26]. Also, the clinical pharmacist could detect DDIs and prevent their actual occurrence[23,29]. Likewise, community pharmacists can manage DDIs in cooperation with local physicians[48]. DDIs result because of healthcare providers' inexperience with pDDIs[33]. Health professionals' awareness about pDDIs and the proper use of medications should be raised to avoid DRPs[21,28,39,42]. Moreover, educating clinical pharmacists could enrich the clinical consequences for patient cases like oral chemotherapy[49]. Electronic systems along with improving healthcare providers' culture regarding reporting and auditing resulted in reduced DRPs rates[43]. This article also outlined mentioned strategies to reduce DRPs rates through optimizing prescription and dispensing processes and using checklists and cognitive aids. The number of pharmacist interruptions should be reduced especially at critical tasks such as prescription or product review[41]. The heavy workload of the pharmacist with unclear job descriptions and responsibilities contributed to DRPs[28]. A recent systematic review agreed with this article. It showed that pharmacist is the drug expert who could improve patient compliance, offer effective medication review, and reduce hospital admission rates[60]. In addition, a new trial demonstrated that pharmacist involvement enhanced the identification of DRPs. A geriatrician and clinical pharmacist tailored the appropriate pharmacotherapy for malignancy associated morbidity. Moreover, multidisciplinary medication review had a positive effect on the detection of DRPs[61].

Furthermore, this review outlined those automated resources improve healthcare services, check prescriptions, and give applicable warnings to avoid probable ADRs to result in diminished ADRs, mortality, and costs[51,55,57]. A systematic review showed that automated systems saved time for physicians and increased adherence to guidelines[62]. Also, electronic resources could minimize both administration and PEs[63]. On the other hand, novel sorts of MEs were reported using electronic systems such as choosing the wrong drugs[54]. Moreover, some drawbacks are incorrect insertion of patient data, delay in medications delivery time due to the slow internet, or the shortage of computers and resulting communication gap between doctors and nurses[51]. Likewise, a narrative review revealed that continual use of electronic resources could lead to infrequent programs related MEs[64]. Our article

demonstrated that these automated approaches needed to be evaluated through further studies[8]. Besides, both optimization of these electronic resources and conducting training programs for healthcare professionals could limit MEs[54].

Conclusions

Many studies focusing on DRPs were published through the specified period. Some showed ADRs and many factors for their occurrence while others illustrated MEs. Also, several studies demonstrated DDIs and revealed them in various specific populations. Both cardiac and psychiatric patients are at high risk of pDDIs. Aging, polypharmacy, co-morbidity, genetic variability in drug pharmacokinetics, drug-specific properties, multiple prescribers at different locations, and hospital stay are risk factors to increase the possibility of DDIs. Polypharmacy was the common predisposing factor associated with DDIs and ADEs were shown to increase the risk of hospital admissions and healthcare costs. The frequently used tools - Beers and STOPP/START criteria - to improve the quality of prescriptions and the use of drugs among the elderly were explained. Patient safety is the responsibility of the whole healthcare team. Efforts to reduce DRPs were elucidated via relying on DDI resources, healthcare providers' training programs, pharmacist interventions, patient education, and automated systems. It is hoped that health policymakers and health professionals will find this data useful in enhancing patients' quality of care.

Conflicts of Interest
The authors declare that they have no conflict of interest.

Ethics Approval
Not applicable.

Consent to Participate
Not applicable.

Consent for Publication
Not applicable.

Availability of Data and Material
The authors confirm that all relevant data are included in the article.

Code Availability
Not applicable.

Authors' Contributions
The five researchers (MGM, MSM, ZAA, YLY, and AIA) evaluated articles for relevance to the objective of the review. (MGM and MAR) were responsible for the inclusion step. In addition, the final review of this article was accomplished by (MAR).

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