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Original Research Article

Enhancing patient safety: leveraging artificial intelligence-powered electronic medical records for effective drug-drug interaction nudge in real-world prescribing practices

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ABSTRACT

Background: Concurrent prescriptions of various medications may lead to unfavorable and unanticipated potential drug-drug interactions. Hence, the elimination of drug-drug interactions is a key aspect of delivering a coherent treatment regime. In response to this concern, HealthPlix, one of India's largest AI-powered electronic medical record providers, introduced a drug-drug interaction nudge feature in June 2022, providing a proactive solution for physicians to address potential interactions between incompatible drugs. This study aimed to elucidate the role of electronic medical records in identifying and managing drug interactions and the advantages of interaction nudges for doctors in prescribing appropriate medications.

Methods: An observational retrospective study was conducted using data obtained from HealthPlix, containing two or more drugs, written for patients older than 18 years.

Results: In an average of 1.9 million patient visits analyzed, the interaction visits were observed to be 1.2 million. An average of 185,745 interactions were observed during the study period. For all observed interactions, an average of 72,383 molecules were removed. These results provide insights into the efficiency of HealthPlix in abrogating interactions and illustrate the tangible benefits of nudges in modifying prescription practices.

Conclusions: The above results illustrate the effectiveness of drug-drug interaction nudges as a clinical decision support tool integrated into HealthPlix, marking a significant advancement in Indian healthcare. This unique feature contributes to reducing the frequency of potent drug interactions, showcasing its potential to enhance patient safety and improve the quality of healthcare delivery.

Keywords: HealthPlix EMR, Drug-drug interactions, Nudges, Real-world

INTRODUCTION

With the abundance of potent drugs available, pharmacotherapy has emerged as a convenient treatment option for a broad array of conditions, even those traditionally managed by other means. Consequently, healthcare professionals commonly prescribe various medications across a spectrum of diseases, ranging from mild to life-threatening. However, this widespread use of pharmacotherapy presents notable drawbacks. The prevalent administration of multiple medications to

patients creates a significant risk for drug-drug interactions (DDIs).¹

DDIs manifest when the pharmacological or clinical response to the concurrent administration of two drugs deviates from the anticipated outcome based on the known effects of each drug when prescribed independently.² DDIs have emerged as a significant public health issue, being among the primary contributors to adverse drug reactions.³ They can alter the diagnostic, preventive, and therapeutic actions of drugs, leading to adverse events such as

treatment failure, medication toxicity, and changes in drug efficacy.⁴ Additionally, DDIs significantly impact healthcare services utilization, particularly hospitalization rates, and impose substantial economic burdens, increasing costs for individuals and healthcare systems alike.⁵⁻¹⁰

Whereas, in routine clinical practice, it is common to prescribe drug combinations that could potentially interact. This balancing act between maximizing therapy effectiveness and ensuring safety is an unavoidable challenge. Moreover, various other factors also influence the incidence and risk of DDIs, such as age, comorbidities, multiple treatments, nutritional status, and genetic makeup of the individuals.¹¹ With these factors being widespread, it is important to identify clinically significant medication-related decision-support systems that can be applied across healthcare settings to reduce the risk of DDIs.

Electronic medical records (EMR) play a crucial role in healthcare settings, especially in DDI. EMRs act as thorough repositories of patient health information, enabling doctors to track, analyze, and mitigate DDIs with greater accuracy. The DDI nudge created in the EMR functions as a dynamic tool for identifying and managing DDIs.

HealthPlix, one of India's largest artificial intelligences (AI)-powered EMR providers, released the DDI feature in June 2022. Physicians leveraged the inclusion of DDI nudges in the HealthPlix EMR platform for better patient management. Such alerts or nudges at the point of care help doctors take the correct course of action during treatment. This study elucidated the role of HealthPlix EMR in efficiently reckoning DDIs and guiding physicians in the form of a nudge at the point of care.

This study aimed to assess the effectiveness, usability, and impact of DDI alerts in HealthPlix EMR on patient safety, clinical decision-making, and healthcare outcomes in a practical clinical setting.

METHODS

Data source

The study utilized data from the electronic medical record (EMR) system owned and operated by HealthPlix Technologies (<https://healthplix.com/>), a leading healthcare technology company in India. HealthPlix's EMR platform has been in operation since 2016, serving the day-to-day operational needs of 16 medical specialties across more than 300 cities in 20 states. The platform captures comprehensive longitudinal clinical information directly from clinical encounters, encompassing demographics, diagnoses, underlying risk factors, prescribed medications, laboratory test results, procedures, functional status, and other pertinent data elements necessary for clinical analysis.

Settings and design

This retrospective, observational study analyzed data retrieved from the HealthPlix EMR platform spanning from July 2022 to July 2023. The study cohort comprised outpatient individuals prescribed at least two medications during treatment. Interaction strengths between the drugs and identifying molecule combinations exhibiting DDIs were derived from reputable secondary sources, including pharmacopoeias.

When two or more medications are entered in the prescription on the EMR, a protocol nudge is displayed on the EMR screen to alert doctors of any potential drug interactions as per the pharmacopoeias. Figure 1 shows the DDI nudges created by the EMR by screening the prescriptions of the patients.

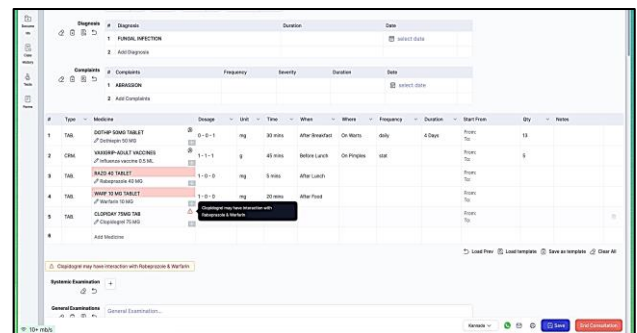


Figure 1: Screenshot of the DDI alert shown in HealthPlix EMR.

Data collection

The collected data encompassed a wide array of variables, including patient diagnoses, demographic information (such as age and gender), and prescribed medications. Specific metrics including the total number of patient visits, frequency of interaction visits, instances of observed interactions during visits, and the number of medications modified or discontinued due to identified interactions were meticulously retrieved and documented in a structured Microsoft Excel spreadsheet.

Statistical analysis

Descriptive statistics were employed to elucidate the demographic characteristics of the total outpatient population, the distribution of prescribed medications, and the characteristics of identified DDIs. To explore potential risk factors associated with DDIs, logistic regression analysis was conducted to calculate the odds ratio (OR) and corresponding 95% confidence interval (CI) based on various patient characteristics. Age categories were delineated as young (18-39 years), middle-aged (40-64 years), and elderly (≥ 65 years) individuals. Statistical significance was set at a p value < 0.0001 . All statistical analyses were performed using the IBM SPSS statistical software package (version 18.0, IBM Corporation, USA).

Data anonymization

To uphold patient privacy and confidentiality, all collected data were anonymized before analysis. No personally identifiable information (PII) or principal investigator (PI) data were utilized in the study, ensuring compliance with relevant data protection regulations and ethical guidelines.

RESULTS

Population characteristics and prevalence of DDIs

Of the visits in the study period from July 2022 to July 2023, 17,88,126 visits exhibited DDIs. Table 1 depicts the

anthropometrics of the study, which illustrates that the study population comprised of 46% of male patients and 54% of female patients. The mean age of the patients was 51 years; 53% of the patients were middle-aged between 31 and 60 years, while older patients (61-90 years) and younger patients accounted for 13% and 33%, respectively. Logistic regression analysis showed that sex and age were independently associated with the occurrence of DDIs ($p < 0.0001$). Male patients had a lower risk of developing DDIs than female patients. Middle-aged and elderly patients were found to have the risk of DDIs increased by 1.88 (95% CI 1.8715-1.8938) and 2.71 (95% CI 2.6998-2.7343), respectively (Table 1).

Table 1: Characteristics of patients with potential drug-drug interactions and factors associated with the presence of DDIs.

Characteristics	No. of patients (%)	No. of patients with DDI (%)	Adjusted OR (95% CI)	P value
Sex				
Male	3,103,569 (46.66%)	552,731 (46.08%)	Reference	
Female	3,542,386 (53.26%)	646,627 (53.90%)	1.025 (1.0210-1.0290)	<0.0001
Others	5,442 (0.08%)	245 (0.02%)	0.2528 (0.2224-0.2873)	<0.0001
Age (years)				
Young (10-30)	1,486,589 (22.35%)	152,557 (12.72%)	Reference	
Middle-aged (31-60)	3,277,925 (49.28%)	633,299 (52.79%)	1.8826 (1.8715-1.8938)	<0.0001
Elderly (61-90)	1,400,020 (21.05%)	390,356 (32.54%)	2.717 (2.6998-2.7343)	<0.0001
Others	486,863 (7.32%)	23,391 (1.95%)	0.4682 (0.4616-0.4748)	<0.0001

DDI- Drug-drug interactions; OR- odds ratio; CI- confidence interval

Table 2: DDI visits and interactions recorded in the EMR during the study period.

Study period	Total no. of visits	Interaction visits	Interactions shown	No. of visits where molecules were removed	Molecules removed	Visit ratio (molecules removed visit/ interaction visit)	% of visits showing interactions
2022-07	1,816,946	28,022	40,179	11,591	16,348	46.87%	1.54%
2022-08	1,940,889	65,291	92,080	26,394	36,857	41.36%	3.36%
2022-09	1,927,152	127,728	178,343	48,181	66,824	40.43%	6.63%
2022-10	1,743,202	103,084	143,842	38,518	53,541	37.72%	5.91%
2022-11	1,876,671	134,047	187,468	49,736	69,415	37.37%	7.14%
2022-12	1,899,438	135,905	191,071	50,109	70,095	37.10%	7.16%
2023-01	1,902,329	161,420	214,294	59,733	83,987	36.87%	8.49%
2023-02	1,943,758	163,089	216,652	60,305	85,041	37.00%	8.39%
2023-03	2,094,030	182,650	242,436	68,244	96,289	36.98%	8.72%
2023-04	1,889,028	167,489	222,404	62,946	88,717	37.36%	8.87%
2023-05	1,925,278	174,250	230,981	64,768	90,716	37.58%	9.05%
2023-06	1,932,236	168,180	222,373	63,437	89,133	37.17%	8.70%
2023-07	2,167,049	176,971	232,574	67,243	94,027	37.72%	8.16%

Interaction visits and interaction analysis

In the average of 1.9 million visits recorded in the EMR during the study period, the average number of interaction visits observed was 1.37 million (Table 2). The number of visits that showed interactions was higher in March 2023. An average of 185,746 DDIs were observed during the

visits during the study period. For all interactions observed in the EMR, an average of 72,383 molecules were removed. The visit ratio for each month during the study period was depicted by the number of visits where the molecules were removed (molecules-removed visits) upon the total interaction visits.

Table 3: Top 10 molecules with high interactions detected by the EMR.

Ranking	Drug	Interactions shown (n)
1	Clopidogrel	215,391
2	Tramadol	189,850
3	Escitalopram	155,029
4	Spironolactone	144,260
5	Rabeprazole	144,086
6	Nortriptyline	129,888
7	Methotrexate	122,072
8	Cholecalciferol	117,936
9	Calcitriol	104,852
10	Amitriptyline	87,548

The top 10 molecules with high interactions are presented in Table 3. Clopidogrel was the top molecule that displayed a high number of interactions (n=215,391) followed by tramadol (n=189,850), escitalopram (n=155,029),

spironolactone (n=144,260), rabeprazole (n=144,086) in the first five places.

Potential clinical consequences of DDIs

Table 4 illustrates the potential clinical consequences and the related mechanisms of the top DDIs. The most frequent pair of DDIs were clopidogrel-rabeprazole (21,640 interactions). The decreased efficacy of clopidogrel in reducing heart attack and stroke is a potential clinical consequence of this interaction. The interactions between telmisartan and spironolactone were also found to be more noticeable (10,746 interactions), which would have a derogatory impact on potassium levels, resulting in hyperkalemia. Methotrexate + pantoprazole, pregabalin + tramadol, glimepiride + fluconazole, and escitalopram + amitriptyline were the other top DDIs for which the alerts appeared in the HealthPlix EMR.

Table 4: Most frequent DDI pairs detected in HealthPlix EMR.

Interacting pairs	N (no. of times)	Potential clinical consequences
Clopidogrel, rabeprazole	21,640	Decreased efficacy of clopidogrel in reducing heart attack and stroke
Telmisartan, spironolactone	10,746	Hyperkalemia, kidney failure, muscle paralysis, cardiac arrest
Methotrexate, pantoprazole	7,170	Renal toxicity, hematologic events, mucositis and myalgia.
Pregabalin, tramadol	6,354	Respiratory distress, coma, CNS depression
Glimepiride, fluconazole	5,656	Hypoglycemia
Escitalopram, amitriptyline	4,333	Serotonin syndrome (confusion, hallucination, seizure, extreme changes in blood pressure etc.)

DISCUSSION

In an age where medication regimes are increasingly complex, the ability to swiftly identify and mitigate potential interactions between drugs is paramount to patient safety. EMR plays a crucial role in DDI alerts by integrating technology into health care. Integration of DDI alerts or nudges into EMR systems represents a proactive approach to minimizing the risks associated with medication management. Within this context, the dynamic DDI nudge feature in HealthPlix EMR empowers doctors by providing real-time access to molecule-to-molecule interactions during patient care.

This retrospective real-world study sheds light on the significance of this integration and the nudges created. Approximately 1.8 million visits showed interactions during the study period. All interactions recorded in the EMR were severe. This underscores the critical importance of leveraging technology, such as EMRs with DDI nudges, to safeguard patient well-being in today's complex healthcare landscape.

The data extracted from HealthPlix EMR revealed that patients within the age group of 31-60 years exhibited

more interactions than other age groups. This finding does not concur with the results of another study in which older patients were associated with a higher incidence of DDI.¹²

Furthermore, the EMR data corroborate with numerous other studies, affirming that polypharmacy (the use of more than three medications per prescription) is a contributing risk factor for the occurrence of DDIs.¹³ The consensus from numerous investigations is that an increase in the number of prescription drugs increases the risk of developing DDI.^{14,15}

In this study, most identified DDIs were associated with medications used to treat conditions such as osteoporosis, cardiovascular disease, gastroesophageal reflux disease (GERD), hypertension, and inflammatory diseases. Specific drugs included clopidogrel, tramadol, escitalopram, spironolactone, rabeprazole, cholecalciferol, esomeprazole, telmisartan, and methotrexate. However, it is important to note that due to variables such as the pattern of drug utilization and sources of drug utilization, several contraindications have been identified in other studies. The study conducted by Diksis et al documented this unpredictability, emphasizing that aspirin, clopidogrel,

and enalapril emerged as the primary drugs associated with potential DDIs among hospitalized cardiac patients.¹⁶

Besides, the EMR data also illustrated that the common interacting pair showing higher nudges with potential clinical consequence was clopidogrel-rabeprazole. This DDI may be attributed to presence of polypharmacy in prescriptions, potentially modulating the pharmacokinetic (PK) and pharmacodynamic (PD) effects of clopidogrel.¹⁷ It is noteworthy that, a reduced clopidogrel-induced antiplatelet effect can lead to thrombotic complications, including acute myocardial infarction or stent thrombosis.¹⁸

The second most clinically relevant DDI alert, as evidenced by clinical data, was spironolactone and telmisartan. Abbas et al reported that an increased prescription of spironolactone spiked the rates of hyperkalaemia when co-administered with angiotensin receptor blocker (ARB) inhibitors with a higher risk in real-world scenarios compared to clinical trials.¹⁹ Additionally, Očovská et al identified spironolactone-telmisartan co-administration as causing evident DDIs, leading to adverse drug reactions documented upon patient hospital admission.¹² The DDI nudge feature, thus integrated into the HealthPlix EMR, underscores the necessity for vigilant monitoring of potassium levels to avert this potentially life-threatening complication, especially at the initial stage of spironolactone prescription and when additional risk factors exist.

The concomitant prescription of methotrexate-pantoprazole also triggered a significant alert in HealthPlix EMR. A study carried out by Bezabeh et al, emphasized the concerning impact of this combination, indicating that concurrent administration of high-dose methotrexate with proton pump inhibitors (PPI) inhibitors (e.g., pantoprazole) may hinder methotrexate elimination, leading to methotrexate toxicity.²⁰ This study also highlighted the importance of physicians being aware of this interaction, given the widespread use of PPI. Furthermore, a recent study indicated that when used together with PPI, lower doses of methotrexate may result in a delayed onset of certain hazardous adverse reactions. The study documented the onset of severe pancytopenia, characterized by low levels of red blood cells, white blood cells, and platelets, occurring in patients 8- and 13-days following administration of low-dose methotrexate and PPI. Additionally, the study also importance of monitoring drug interactions despite normal renal function.²¹

Pregabalin-tramadol and glimepiride-fluconazole were the other important combinations for which the EMR flagged a DDI alert, prompting a nudge. The pregabalin-tramadol interaction was found to be associated with central nervous system (CNS) depression and was categorized as a severe DDI. This was elucidated in a study investigating the detection of DDIs in patients with ovarian cancer in tertiary care. Among 92 patients, interactions between supportive therapies were recorded, with the pregabalin-

tramadol combination identified as one of the major DDIs.²²

Similarly, Tirkkonen et al reported in their research that the CYP2C9 inhibitor fluconazole was found to prolong the elimination phase half-life and increase the maximum plasma concentration of glimepiride, leading to hypoglycaemia, rendering the combination fatal.²³ The EMR also displayed an interaction nudge on escitalopram-amitriptyline co-prescription. This may be ascribed to pharmacodynamic interactions that are more likely to cause serotonin syndrome and increased bleeding, which was articulated in a review of antidepressant drug interactions by Bleakley.²⁴

Collectively, the observations of this study highlight the outcomes derived from our extensive EMR data on the DDI phenomenon, aiming to generate practical interventions for the promotion of public health. This accentuates the pivotal role of HealthPlix as a comprehensive platform for correlating and analyzing patient data with DDI nudge information, enabling data-driven comparative approaches to detect, predict, and explain diagnostic outcomes.

However, our study had some limitations. This retrospective study did not assess the clinical consequences of DDI. It was presumed that the prescribed drugs were administered for the entire duration of treatment. However, in reality, patients may discontinue the treatment course, and doctors may substitute medications for patients complaining about side effects. The study did not examine any side effects before or after the nudge. DDI override circumstances were also not recorded in the study, the inclusion of which might enrich the analysis in a critical context.

CONCLUSION

These findings underscore the complex nature of drug interactions and the need for tailored medication management strategies. The integration of DDI nudges into EMR system, as demonstrated in this study, has emerged as a critical tool which would enhance patient safety and optimize healthcare outcomes. The nudges displayed by the HealthPlix EMR serve as real-time warnings that notify doctors about potential interactions between prescribed medications. By flagging combinations that could lead to harmful effects or reduced efficacy, DDI nudges of the EMR platform empower physicians to make informed decisions and adjust treatment plans accordingly. This proactive approach helps prevent dangerous drug interactions, thereby safeguarding the well-being of patients and enhancing the overall healthcare quality.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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