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ORIGINAL RESEARCH

Role of Free Web Based Software in evaluating the profile of Drug -Drug Interactions

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ABSTRACT:
Background: Utility of web-based free drug interactions software in clinical practice can prove very useful to enhance drug safety but remain less studied.
Objective: To analyze the role of free web based software in evaluating potential DDIs in the prescriptions prescribed in tertiary Care Teaching Hospital.
Method: The utility of information retrieved for every drug for respective DDIs picked up by Free web based software (Healthline drug Interaction Checker) was compared with standard references (Stockly's Drug Interaction and Goodman and Gillman's Pharmacological Basis of Therapeutics) to work out sensitivity, specificity, positive predictive value and negative predictive value of the software in picking up of potential DDIs.
Results: A total number of 500 prescriptions prescribed for any medical condition were collected randomly from different departments for one-point analysis. A total number of 1861 drugs were prescribed with an average of 3.72 drugs per prescription. A total number of potential 3230 DDIs were studied and analyzed. 560 (17.34%) DDIs were picked up by the software. Goodman Gillman's Textbook validated 43.84% interactions, while Stockly's Textbook validated 55.67% interactions. Correlation for DDIs of software was better with Goodman Gillman's textbook as compared with Stockly's Textbook for Sensitivity (90% vs 61.42%), specificity (65.84% vs 45.88%), positive predictive value (35.59% vs 19.22%) and negative predictive value (96.91% vs 85.01%).
Conclusion: The study observed that validation of potential drug-drug interactions picked-up by the Free Online software was suboptimal as per sensitivity, specificity and accuracy was concerned and thus cannot be recommended to clinicians.
Key Words: Drug - Drug Interaction, Free Web-based Software, Drug Information

Introduction

Drug interactions (DDIs) results in many adverse clinical outcomes.They are responsible for 5% of all hospital admissions [1]. Incidence of potential DDIs ranges from 2.2 to 30% in hospitalized patients and 9.2 to 70.3% in ambulatory patients [2].
Furthermore, 3 to 5% of all in hospital medication errors result from DDIs and are important cause of patient visit to emergency department. Adverse DDIs are a major cause of morbidity and mortality worldwide[3].
The incidence of adverse drug events as a result of DDIs is increasing in the day-to-day clinical practice as a result of irrational drug use, polypharmacy and self-medication. Besides this, many a times comprehensive treatment of a diseases may require use of more than one drug or sometimes patient with multiple symptoms and co-morbid conditions are prescribedmore number of drugs raising the possibility ofDDIs even if drugs are prescribed rationally [4].

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Utility of web-based free drug interactions software in clinical practice can prove to be of immense importance not only in rationalizing and enhancing patients' safety but also in prescribing and dispensing safer drugs [5].

There are many DDIs software's available but their utility and validity still remains very less studied [6], although few studies have suggested that the use of DDIs compendia can improve medication &patients' safety [7, 8].Hence, the current study was done to analyze the role of free web based software in evaluating potential DDIs in the prescriptions prescribed in tertiary Care Teaching Hospital.

Material And Methods

The present study is an observational cross-sectional, prospective, web-based prescription audit study, undertaken after Instructional Ethics Committee clearance vide No: - IEC/2015/142, dated 19-5-2015 and after administrative approval. Audit was carried out over a period of one year in tertiary care teaching hospital and from adjoining hospitals in Jammu region.The prescriptions were collected by an independent person by clicking pictures by, mobile phone outside medical emergencies, out-patient and in-patient departments, without the knowledge of prescriber to avoid any bias.A total of 500 prescriptions prescribed for any medical condition were identified and collected for one-point analysis.

Inclusion Criteria:

- Any prescription medicine prescribed in medical outpatient department, inward patients and medical emergencies.
- Both sexes of any medical conditions.
- Any socio demographic profile.
- Any acute, chronic medical illness.
- Any route of drug administration oral or parenteral.
- Any fixed drug combination.

Exclusion Criteria:

- Self-medication
- Herbal drugs
- Over the counter drugs
- Vaccines
- Nutraceuticals

Sociodemographic profile of patient, background information, health disorders, average number of drugs per prescription with correct dose, strength and dose schedule, number of prescriptions mentioning duration of therapy, overprescribing, banned drug formulation/drug combination with disputed pharmacological rationale, generic prescribing and fixed drug combination rate were evaluated.After categorization of medicine, related data, other medical conditions (acute or chronic), history of smoking, alcohol. Any substance abuse was noted down.

Every medicine prescription was noted individually by generic name in every prescription and was evaluated by the help of commonly used free web-based drug-drug interaction software available on internet.

The selection of free software was based on preliminary survey carried out by giving a questionnaire asking most commonly used drug interaction software (*Healthline Drug Interaction Checkers*) for assessing drug interactions by the prescribers at our set up.

As per the information retrieved by this software, drug interactions were categorized under following heads as:

- Pharmacokinetic
- Pharmacodynamic and pharmaceutical

Subsequently the nature and severity (synergistic, additive or antagonistic) of drug-drug interactions were noted. If pharmacokinetic, then the process which was altered i.e., absorption, distribution, metabolism and excretion were noted. If pharmacodynamic, drug interactions, the detailed mechanism were noted whether it is physical, chemical, enzymatic or receptor level modulation.

The DDIs were also noted down for any of the following three possible outcomes i.e.

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- Increased therapeutic effect
- Adverse event
- Decreased therapeutic effect or a unique response

The DDIs were classified as mild, moderate and severe according to their severity and undesirable effects [9]. Mild drug interactions limit the clinical effects. The manifestations include an increase in the frequency or the severity of the adverse effects, but these usually do not require a change in the therapy. Moderate DDIs may result in exacerbation of the disease of the patient and/or a change in the therapy. The severe drug-drug interactions are life threatening and/or they require medical treatment or an intervention to minimize or to prevent the severe adverse effects.

The possible drug interactions of any drug in prescription with alcohol, smoking or any substance abused was recorded only in mentioned prescriptions.

Finally, to validate the utility of information retrieved for every drug for respective drug-drug interaction was compared with standard references (Stockly's Drug Interaction and Goodman and Gillman's Pharmacological Basis of Therapeutics) to work out sensitivity, specificity, positive predictive value and negative predictive value of the software in picking up of potential DDIs.

All principles of bioethics were adopted. Verbal informed consent was taken as present study falls in least risk category and is an observational (as per ICMR research code)

Name of the drug was identified by generic name. name of the prescriber and the name of the patient was coded for al practical purposes to avoid any conflict of interest.

Statistical Analysis

The data collected was presented in the form of tables and graphs. All data were reported as frequency/percentage. The analysis was carried out with the help of computer software's MS Excel and IBM SPSS version 23 for windows to evaluate specificity, sensitivity, positive predictive value, negative predictive value, accuracy with Mathew correlation Coefficient and other tests.

Results

A total number of 500 prescriptions prescribed for any medical condition were collected randomly from different departments for one-point analysis. A total number of 1861 drugs were prescribed with an average of 3.72 drugs per prescription. A total number of 3230 drug-drug interactions were studied and analyzed. 560 (17.34%) drug-drug interactions were picked up by the software (Healthline drug Interaction Checker). Point prevalence of potential drug-drug interaction with Goodman Gillman's reference textbook was 15.60% and with Stockly's as reference textbook was 10.65% in the current study. Point Prevalence of drug-drug interactions with the Stockly's as reference textbook was 10.65% in the current study. The mean age of the study population was 43.34 years with a range of 1 day to 90 years with male subjects being predominant in the study and female to male ratio being 1.45:1. Adult population predominated in the present study followed by geriatric and pediatric population. Urban to rural population ratio was 1.86:1. History of smoking and alcohol was mentioned in 5.80% and 6.20% prescription analyzed. Primary/provisional diagnosis was mentioned in 91.60%. Diabetes mellitus was mentioned in 16% prescriptions, hypertension in 13.40%., pain abdomen in 5.40%, ischemic heart diseases with myocardial infraction in 4.80%. Co-morbid conditions were mentioned in 43.20% prescriptions, which included type 2 diabetes mellitus in 15.40%, hypertension in 13.40%, hypothyroidism in 2.60% subjects. Dose used was prescribed for 75.33% drugs, route for administration for 99.23% drugs, dosage form mentioned for all 100% drugs, duration of treatment was mentioned for 17.99% drugs and dosage schedule was mentioned for 99.97% drugs, out of 3230 drugs analyzed. Prescription analyzed were from the medicine department (22%), followed by endocrinology (14.40%), Cardiology (13.60%), Pediatrics (12.60%), Surgery (10.60%), etc. (*Table-1*)

Software randomly picked up 560 (17.34%) drug-drug interactions out of 3230 possible drug-drug interactions. Standard reference textbooks Goodman Gillman validated 504, while Stockly's validated 344 drug-drug interactions out of 560 picked up by the software. Out of the total 560 drug-drug interactions, 23.03% drug-drug interactions were graded as mild, 63.75% as moderate and 13.215 as severe by the software. Software detected 377 (67.32%) pharmacodynamic interactions, which included 50.36% receptors, 10.53% enzymatic and receptors and 6.07% only enzymatic. Software

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detected 278 (49.64%) pharmacokinetic interactions, which included elimination 12.50%, metabolism 12.14%, absorption 10.35%, etc. Potential drug-drug interactions were present in relation to food in 22.325 cases, with alcohol in 78.58% cases and with smoking in 27.50% cases. 82.14% drug-drug interactions were rated as harmful, 11.07% as beneficial and 6.79% rated as others. Therapeutic effect was decreased in 82.14% drug-drug interactions, increased in 11.07% and rated as others in 6.79% interactions. Adverse events were found in 91.61% drug-drug interaction, while in 65% drug-drug interactions therapeutic effect was rated as unique response. (*Table-1*)

Out of 3230 drug-drug interactions observed in the study, Goodman Gillman's Textbook validated 43.84% interactions, while Stockly's Textbook validated 55.67% interactions. Correlation for drug-drug interaction of software was better with Goodman Gillman's textbook as compared with Stockly's Textbook for Sensitivity (90% vs 61.42%), specificity (65.84% vs 45.88%), positive predictive value (35.59% vs 19.22%) and negative predictive value (96.91% vs 85.01%). (*Table-2 &3*)

Table-1 Prescriptions and Drugs Prescribed

Total Number of Prescriptions Studied	500
Mean Age of Study Population	43.34 years
Male : Female Ratio	1:1.45
Total Number of Drugs Prescribed	1861
Average Number of Drugs Prescribed per prescription	3.72
Total Number of Possible Potential DDIs analyzed	3230
Total Number of Potential DDIs picked up by software	560
Severity of Picked up Potential DDIs	Mild (23.03%); Moderate (63.76%); Severe (13.21%)
Type of Potential DDIs	Pharmacodynamic (67.32%); Pharmacokinetic (49.64%)
Beneficial Vs Harmful Vs Other	11.07% Vs 82.14% Vs 6.79%
Adverse Event	Present (91.61%) Vs Not Present (8.39%)
Therapeutic effect	Increased (11.07%) Vs Decreased (82.14%) others (6.79%)
Point prevalence of DDIs	17.34%
Validated by Goodman Gilman's Textbook	504
Validated by Stockly's Textbook	344

Table -2 Relation of Potential Drug-Drug Interaction Picked Up by the Software and Validated by Goodman Gillman's Textbook

True Positive; True Negative; False Positive; False Negative	504; 1758; 912; 56
Sensitivity	504/ (504+56) =90%
Specificity	1758/ (1758+9120=65.84%
Positive Predictive value	504/ (504+912) =35.59%
Negative Predictive Value	1758/ (1758+56) =96.91%
False Positive Rate (FPR)	34.16
False Negative Rate (FNR)	10
False Discovery Rate (FDR)	64.40
Accuracy	70.03
F1 Score	51.01
Matthew Correlation Coefficient	0.00
Markedness	-161.32
Power	90

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Likelihood Ratio Positive	2.64
Likelihood Ratio Negative	0.15

Table 3. Relation of Potential Drug-Drug Interaction Picked Up by the Software and Validated byStockly's Textbook

True Positive; True Negative; False Positive; False Negative	344;1225; 1445;216
Sensitivity	344/ (344+216) =61.42%
Specificity	1225/ (1225+1445) =45.88%
Positive Predictive Value	344/ (344+1445) =19.22%
Negative Predictive Value	1225/ (1225+216) =85.01%
False Positive Rate (FPR)	54.12
False Negative Rate (FNR)	38.58
False Discovery Rate (FDR)	80.78
Accuracy	48.58
F1 Score	29.29
Matthew Correlation Coefficient	0.00
Informedness	7.30
Markedness	-165.79
Power	61.43
Likelihood Ratio Positive	1.14
Likelihood Ratio negative	0.85

Discussion

The performance of DDI-detecting software programs was suggested suboptimal by Hazlet TK *et al.*[10] like our study. The software systems failed to detect clinically relevant DDIs one-third of the time in their study. Sensitivity of the software programs ranged from 0.44 to 0.88, with 1.00 being perfect; specificity ranged from 0.71 to 1.00; positive predictive value ranged from 0.67 to 1.00; and negative predictive value ranged from 0.69 to 0.90.

The results of the current study are almost similar to the findings of the study of Robert D. Beckett RD *et al.*[11], where in the utility of various DDIs software were studied and the results suggested that Scope scores ranged from 0.6% (Drug Interactions Analysis and Management) to 43.4% (Lexicomp Online). Completeness scores ranged from 2 (interquartile range [IQR] 0 to 3, Stockley's Drug Interactions) to 5 (IQR 5 to 5, Drug Interaction Facts, Micromedex, Facts & Comparisons eAnswers). Consistency scores ranged from 30.8% (Stockley's Drug Interactions) to 87.1% (Clinical Pharmacology) for severity and from 15.4% (Facts & Comparisons eAnswers) to 71.4% (Drug Interaction Facts) for course of action. Thereby, suggesting DDIs interactions was low and content was often inconsistent among resources, like our study.

The study of Shariff A *et al*[12], suggested that the inter-source reliability scores among the eight different DI sources were poor ($k < 0.20$, $p < 0.05$) for documentation of information related to severity, clinical effects, mechanism, and management of DDIs. Variations in the information cause uncertainty among healthcare professionals concerning interacting drug pairs in clinical practice. This may also increase the possibility of adverse drug outcomes when interacting drug pairs are used in at-risk patients.

In a systematic review, utility of various software was studied and like the results of our study deficiency of clinical relevance was suggested to be major draw back of these software in providing DDIs Information [13].

Similarly the study of Barrons R [14]suggested that all drug interaction resources suffer from limitations in the quality or relevance of evidence for the interaction, an absence of identifiable patient and medication risk factors, and a lack of standardization in assigning significance to the interaction.

Conclusion

The study observed that validation of potential drug-drug interactions picked-up by the software was suboptimal as per sensitivity, specificity and accuracy was concerned. Hence, at present the said

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software cannot be advocated to healthcare providers for complete evidence-based, scientific information related to potential drug-drug interactions.

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