COMPARISON OF VARIOUS SOFTWARE PROGRAMS IN DETECTING POTENTIAL DRUG-DRUG INTERACTIONS AT COMMUNITY PHARMACY SETTING

INTRODUCTION

Drug-drug interactions (DDI) considered as drug related problem which could be resulted in severe consequences. Hospital admission, death, disability, organ failure, and congenital abnormalities would be raised with DDIs. Therefore, evaluation and determination of the possible DDIs would be essential.

It was determined that drug-drug interactions could be still resulted in risk according to result gathered from reason of admission to emergency departments [1]. To eliminate the number and possible detriments of DDIs, pharmacists should be aware of these possible DDIs and must evaluate clinical relevance of each DDI. Pharmacists should be involved in optimizing medication treatment by preventing harmful drug-drug interactions and unsafely utilization of medication. However, pharmacists exposed to numberless warnings including many minor and moderate interactions while using programs and/or software to detect possible drug-drug interactions. As consequences of that, major drug-drug interactions could be ignored [2].

The reliabilities of software programs commonly used to detect possible drug-drug interactions have been evaluated and the concordance rate between each other have been also investigated. The criterion of many drug-drug interactions has not been standardised for every software programs. Therefore, some of software programs contained too much data. So that, most of time; it is hard to distinguish clinically significant information from others [3].

In one of the drug utilization review study retrospectively conducted with high patient population, it was obtained that possible number of DDIs detected at baseline, has been decreased in a ratio of 70.8% after applying more sophisticate filtration and it was also observed that these number has been reduced in a ratio of 80.6% after evaluation of clinical pharmacist [4].

In many studies compared these DDI software programs, it was point to inconsistency problem between these programs. In these studies, it was mostly

preferred DDI software programs which generally used with subscription and required paid membership, and also in these study researchers especially chose the one that had their institutional subscription. However, fewer ones evaluated some web sources which could be accessed freely.

Patient oriented services including clinical pharmacy and pharmaceutical care has been recently developed in Turkey. As concordance with this development, it will be concluded that community pharmacists' skill to check possible drug-drug interactions is still progressed slowly.

Although there are many DDI checker program in literature and practical applications, Micromedex and Lexicomp are commonly used programs due to offer strong and comprehensive evidences including onset, severity, scientific evidence, pharmacologic effects, mechanisms of action, and management of each drug-drug interactions. In development countries, Medscape Drug Interaction Checker and the Monthly Index of Medical Specialties Interaction Checker which can access without paying any charge are commonly preferred rather than Micromedex and Lexicomp [5].

In the present study, it is aimed to compare Micromedex with two web based programs freely accessed (Medscape Multiple Drug-Drug Checker and drugs.com) to investigate whether one software program is enough to determine possible drug-drug interactions at community pharmacy setting or not. The result of the present study would be important when establishing guideline to determine drug-drug interaction at community pharmacy.

MATERIALS and METHODS

The prescriptions have been collected from 50 community pharmacies located in Istanbul between March and April 2015 (two days/ a week). These pharmacies have been chosen from the ones where the fifth-grade pharmacy students went to complete their 'Pharmacy Practice' course. The oral and written consent has been received from pharmacist after given information regarding the aim and methods of the present study. The ethical approval has been taken from xxxxxx University, Institute of Health Science.

The first twenty prescriptions included more than one drug have been collected to evaluate potential drug-drug interactions from each pharmacy by

students. If the prescription belonged to patient aged under 18 years old; these ones would have been excluded from the study.

Patients' demographic information including age and gender has been recorded. The prescriptions included any drugs that have not been involved in the software programs, have been excluded.

The following software programs were utilized to detect potential drug-drug interactions, 'Micromedex 2.0® Software Drug Interactions', 'Medscape Drug Interaction Checker®', and 'drugs.com' (Table 1). The possible drug-drug interactions were analysed retrospectively. The interactions were reported as major or serious, moderate or significant and minor or mild interaction (Table 1).

Statistical Analysis

Continuous variables were presented as mean±standard deviation and ordinal and nominal data were shown as number [n] and percentage [%]. The correlation between data has been investigated by using spearman correlation test. The concordance between these online drug interaction programs according to the results of three severity levels of interaction has been checked by evaluating each drug-drug interaction by using Kappa analysis. The statistical analysis has been done by using SPSS (Statistical Package for Social Sciences) for Windows 11.0. $p<0.05$ was defined as the level of statistical significance.

RESULTS

In each prescription, the mean number of medication was calculated as 3.01±1.19 (2-10). At least one potential drug-drug interaction has been detected in 39.2% of a total of 1000 prescriptions by using at least one-software program. More than half (58.7%) of the prescriptions that detected at least one potential drug-drug interactions belonged to female patients. Moreover, the mean of age of these patients was 54.63±17.20. According to the rates of total drug-drug interactions gathered from various software programs, these software programs were arranged as 'Medscape Drug Interaction Checker®' (33.3%,), 'drugs.com' (31.3%), and Micromedex 2.0® Software Drug Interactions' (21.2%). A total number of DDIs in Micromedex 2.0® Software Drug Interactions', 'Medscape Drug Interaction

Checker®', and 'drugs.com' detected were 389, 917, and 670; respectively. The rate of DDIs detected in prescriptions with all programs was %18.

When considered the programs in two pair comparison, the concordance rate was found high and kappa coefficients were measured as moderate level (Table 2).

The concordance rate of three programs (which is defined as detecting the number of patients w/who DDI at the same time) was 78.9%; and this rate was found lower than the concordance rates obtained in two pair comparison; which was shown in Table 2.

When considering two pair correlation between the programs, Spearman r correlation values were measured 0.629; 0.711, and 0.688 ($p<0.001$); respectively. These results concluded that two pair correlations were moderate.

To measure severity rankings of three DDI programs, the total number of DDI without repetition (the number of DDI was considered as one if the same DDI obtained more than one patient or if the same DDI with different mechanisms considered as more than one DDI) obtained in these three programs in 1000 patients, was calculated. The total number of DDIs was calculated as 625 according to above statement. The rate of these DDIs obtained in Micromedex 2.0® Software Drug Interactions', 'Medscape Drug Interaction Checker®', and 'drugs.com' was 42.2%, 65.6%, and 74.1%; respectively. The severity ranking scored by three programs for these 625 DDIs was found dissimilar (Table 3).

When evaluating the two pair concordances in programs according to severity ranking none of them was obtained higher than 50% (Table 4). It was determined that eighty-two (13.1%) of them have been scored with the same severity level in both three programs among a total of 625 DDIs. The most of them (68) among these 82 DDIs were ranked as moderate DDI. The major DDI classified as major by Micromedex was found 89 and the only twelve of them was defined as major DDI with the other two DDI programs used in the present study.

When considering two pair correlation between three programs according to severity ranking, Spearman r correlation values were calculated 0.222 ($p<0.001$); 0.366 ($p<0.001$), and 0.061 ($p=0.125$); respectively. These results concluded that two pair correlations were moderate.

DISCUSSION

In the literature, the studies that evaluated more than one DDI software programs usually emphasized the difference between each software programs that were compared especially on their severity classifications. However, the three DDI software programs evaluated in the present study had similar classification system when evaluating the clinical consequences of each possible DDI. Community pharmacists would prefer mostly the freely accessible DDI software programs because of concern regarding economic issues. On that purpose, the two web-based DDI software program have been chosen in the present study. To compare these programs, Micromedex which is utilized as comprehensive drug information sources had been selected. In this study researchers' university library had subscription to Micromedex and in the present study conducted during fifth grade students' pharmacy courses, as a part their assignment during this course, all students could subscribe Micromedex and could checked possible DDI in the prescriptions. The 1000 patient prescriptions selected and analysed by researchers again on the purpose of the present study.

In the present study which assessed possible DDI in 1000 patient prescriptions at community pharmacy setting with three DDI software programs, it was found that Micromedex detected possible DDI in less number of patients (21.2%) when compared with other software programs. And also, when compared the total number of possible DDI in each program obtained, Micromedex detected a half number of other two DDI software programs obtained. Medscape DDI checker software evaluated separately each DDI with attributed more than one mechanism and scored with several severities. This discrepancy would be caused by the fact that in Medscape, it was determined as separate drug-drug interaction in case where more than one mechanism were occurred. Moreover, the number of minor interactions found in Medscape is higher than the other program. This could be reason for higher the total number of possible DDI in Medscape obtained.

Similarly, Oshikoya et al obtained a total of 596 potential DDI in 280 patients with HIV and 84.6% of them detected in Medscape and only 50.7% of them obtained in USA MIMS (Monthly Index of Medical Specialties Interaction Checker) [5]. The rate of drug-drug interaction was found 46.1% and the correlation between severities score was determined as weak.

Olvey et al. compared Micromedex with two standard software programs: DRUG-REAX and Drug Interactions: Analysis and Management (DIAM) by analysing drug-drug interaction lists in US Department of Veterans Affairs (VA). According the result of this study, it was obtained that 13.7% of a total of 982 drug-drug interactions which considered as critical by VA detected in all three software programs and also the concordance between programs was determined as a low [6].

In the present study, the rate of DDIs detected in prescriptions with all programs was %18. Binary concordance rates based on number of patient prescription obtained by DDI software programs calculated approximately 84-88% and Kappa coefficient between 0.6 and 0.7. On the other hand, when analysed all of them, the concordance rate was measured under the 80%. These results and correlation values presented that there was a moderate concordance between all three DDI software programs according the number of patient prescriptions. When compared with other studies, the concordance rate was found higher in the present study. Vonbach et al. found a total of 157 DDI by using Drug Interaction Facts, Drug-Reax, Lexi-Interact and Pharmavista and the only 11% of them detected by all of the DDI software programs. In this study, none of the DDI software programs could determine more than 50% of a total DDI [3].

Bergk et al. determined that 33% of them was similar in all DDI programs when compared clinically significant DDI by utilizing German SmPC, DRUGDEX, Hansten/Horn's Drug Interaction Analysis and Management, and Stockley's Drug Interaction programs [7].

Chao and Maibacj compared four DDI compendia (Mosby's GenRx, USP DI, AHFS Drug Information, and the Physicians' Desk Reference) most commonly utilized in USA in their study by screening DDIs, the most prescribed 4 medications involved in dermatology services and these programs found incompatible. The concordance rate found reduced when compared more than two software programs.

The only 8.9% of total number of DDIs achieved in all four DDI compendia. Therefore, Chao and Maibacj suggested reassessment of these programs according to information in literature and clinical relevance of each DDI [8].

In the other study that compared BNF with Medicine Compendia (eMC) and DailyMed programs, it was found that BNF obtained two-fold more DDIs when compared with DailyMed and 63.9% of them found with only one compendia and the rate of DDI detected in both three compendia was 15.12% [9]. The weak correlation coefficient (0.366) has been measured between three compendia. It was stated that this incompatibility was caused by the difference between drug classification in three systems and also the source of DDI in programs not presented [9].

The difference in a total number of possible DDIs did not cause this discordance between most of various DDI program and it was suggested that this could be also caused because of difference in severity classification in these programs [10-13].

The concordance between DDI programs used in the present study was high in the point of the number of patients detected possible DDI in each program when compared with previous studies mentioned above. Although DDI programs used in the present study were quite similar to each other according to severity classification of possible DDI, the concordances regarding rate of severity ranking were low. The rates of concordance in two pair comparison of DDI programs were approximately less than 50% and also Kappa coefficients were relatively low in the present study. The only 13.1% of a total of 625 DDIs has been scored with the same severity level in both three programs. The major DDI classified as major by Micromedex was found 89 and the only twelve of them was defined as major DDI with the other two DDI programs used in the present study.

Vitry et al. found the rate of major interactions obtained at least one program was between %14 and 44% when compared four different programs and mentioned irreconcilable between programs according to the grading of the severity and the quality of the supporting evidence of them [14]. Vitry et al. stated the reasons of this discordance between programs as various inclusion criterions and different information sources, and dissimilar therapeutic drug classification in each program

used, and also severity classification based on clinical relevance of each DDI was not common in programs [14].

Ekstein et al. found more than 30% of interactions in at least one program when compared three different DDI programs according to antiepileptic drugs in their study. In this study, the concordance rate was less than 30% even if severity levels were classified as high between programs. These discrepancies would be attributed to difference in definition and terminology in each program, various clarification of information in literature, different classification of drugs were used in various DDI programs [15].

It is well known that DDI programs should be more sensitive and specific for practical usage of pharmacists [16,17]. Reis and Cassiani compared DDI programs by selecting one of them as gold standard and calculated sensitivity and specify of DDI programs [18]. In this study, it was emphasized on limitations of DDI programs and suggested essentially evaluation of DDI programs which was chosen for detection of possible DDI at hospital setting [18].

Some of the possible DDIs were definitely different between programs in the present study. For example, some of the experts accepted as polypharmacy if two NSAIDs were available in the same prescription. Only Medscape warned as moderate (significant) interaction for this situation when DDI programs used in this study are considered. The other programs did not obtain any interaction between two NSAIDs if they were prescribed concurrently. Discordance between programs would be slightly attributed to this kind of interaction which was obtained in twenty-one of 1000 patients in the present study. All these discrepancies were questioned which DDI program would be selected as gold standard when sensitivity and specificity of DDI programs is evaluated.

Based on the result of present study and other studies in literature, it should be re-evaluated DDI programs to improve concordance of them by assessing evidence based outcomes and severity classification. According to the report of consensus panel where it was evaluated, evidences of DDI in the process of clinical decision, the following statements were offered to obtain high qualified information from DDI programs: the consistent terminology should be constituted, ‘Drug Interaction Probability Scale’ should be utilized to assess case reports regarding possible DDI,

the new approach should be formed to evaluate evidence regarding DDI, the assessment of FDA documents and drug leaflets should be performed with the same criterion like evidences reported, and when the evidence detected, this possible DDI should be classified according to therapeutic/pharmacology groups [19].

The following suggestions would be offered to improve patient safety: the well-designed studies should be conducted to determine the incidence, outcomes and also patient related risk factors of DDI, algorithms would be produced for defining systematic and clearly process of assessing evidences to evaluate risk and severity of possible DDIs, and the evidences of possible DDIs would be integrated into electronical systems [20].

Because of discordance between DDI programs, when the pharmacists detected major DDI and/or any DDI in clinically critical patients, they should confirm that with another DDI program. Although it seems time consuming, this could be resulted in elevated patient safety. Therefore, it was suggested that health care providers should check possible DDIs with more than one DDI program in clinically critical patient such as patients with HIV.[5]

Limitation of the study

In the present study, the only three software program has been used; because software programs that were chosen in the present study had similar severity classification properties and two web based software used in the present would be freely accessible in worldwide including Turkey. One of the limitations of the present study was unused of 'Rx Media Pharma' which was the most commonly utilized Turkish drug information sources in the present study and is not a free source. The number of the prescriptions analysed in the present study was large. This attributed to evaluation of different medications and diseases with a large number of them. Although this would be advantage to assess possible drug-drug interactions comprehensively, some of the experts could seems that a limitation of the present study because the lack of demonstrating the concordance between special medication groups such as antiepileptic, antidepressant, and anticoagulant.

Conclusion

The high rate of potential drug-drug interactions detected at community pharmacy setting in the present study. After comparison of various software programs, it was found that potential drug-drug interactions gathered from various software programs were different between each other. Therefore, pharmacists could concurrently use more than two various software programs to evaluate and manage potential drug-drug interactions according their clinical impacts.

Conflict of Interest

None

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Table 1. Characteristics of DDI Software Programs

Programs	Access/ payment	Classification	Reference	Addition interactions
Micromedex	Required	0: None, 1: Minor, 2: Moderate, 3: Major, 4: Contra-indicated	Yes, with quality of evidence	Yes, with alcohol, diseases, lab test, pregnancy, food
Medscape	Not required	None, Minor, Significant (Monitor closely), Serious (Use alternative), contra-indicated	No	No
Drugs.com	Not required, also with customer information	None, Minor, Moderate, Major	Yes	Yes, with food

Table 2. Concordance rate obtained with two pair comparison according to the number of DDI gained in prescriptions in three programs.

Program	Concordance (%)	Kappa coefficient	Standard error	*p*
Micromedex - Medscape	83.9	0.601	0.027	<0.001
Micromedex – Drugs.com	87.6	0.686	0.025	<0.001
Medscape – Drugs.com	86.3	0.688	0.025	<0.001

Table 3. Severity ranking of software programs according to 625 different DDI

Programs	Severity Ranking n (%)				
	0 (Not found)	1 (Minor)	2 (Moderate or significant)	3 Major or Serious)	4 (Contra-indicated)
Micormedex	361 (57.8)	10 (1.6)	162 (25.9)	89 (14.2)	3 (0.5)
Medscape	215 (34.4)	74 (11.8)	302 (48.3)	32 (5.1)	2 (0.3)
Drugs.com	162 (25.9)	62 (9.9)	360 (57.6)	41 (6.6)	*

* The severity classification of drugs.com was not contained 4; which was defined as contraindicated.

Table 4. Concordance rate obtained with two pair comparison according to the rate of severity ranking obtained among 625 DDIs in three programs.

Program	Concordance (%)	Kappa coefficient	Standard error	*p*
Micromedex - Medscape	38.9	0.083	0.027	0.001
Micromedex – Drugs.com	45.6	0.211	0.025	<0.001
Medscape – Drugs.com	35.9	-0.029	0.029	0.286