# Large-Scale, Community-Based Trial of a Personalized Drug-Related Problem Rectification System

Natan R. Kahan, PhD, RPh, MHA; Dan-Andrei Waitman, MD, MPH; Matityahu Berkovitch, MD; Shimona Yosselson Superstine, PharmD, MPH; Jacob Glazer, PhD; Abraham Weizman, MD; and Roni Shiloh, MD

## ABSTRACT

**Objectives:** The risk of clinically significant drug-related problems is a major concern, particularly among elderly, polypharmacy-treated patients. Previous efforts to develop computerized alert systems have shown limited effectiveness. The purpose of this study was to evaluate the efficacy of a novel technology, the Drug-Drug Interaction Plus (DDI+) decision support system, used in a real-world ambulatory health maintenance organization (HMO) setting and developed to overcome the limitations of currently available programs.

**Study Design:** Controlled trial.

**Methods:** We conducted a controlled trial of the DDI+ system in Leumit Health Services (LHS), an HMO in Israel that provides coverage to approximately 700,000 members with approximately 2000 physicians nationally. All LHS physicians were geographically allocated by region to a study or control arm. Physician access rates, alert resolution rates, and resource utilization of their patients were evaluated and compared between the intervention and control arms.

**Results:** There were 5.6% ($P$ = .001) fewer mean episodes of hospitalization, 1.5% ($P$ = .01) fewer mean drugs dispensed, and 2.1% ($P$ = .055) fewer mean episodes of imaging in the intervention population versus controls. Drug-related problems that were re-encountered were often rectified without re-accessing the system.

**Conclusions:** Comparing the acceptance by physicians of the DDI+ system to reports of acceptance of similar systems, DDI+ was observed to be better accepted. This will possibly initiate improvements in resource utilization patterns. We surmise that improved physician willingness to access the system can be attributed to the novel graphic presentation, specificity, and integration of DDI+ into the work flow of routine clinical practice.

*Am J Pharm Benefits. 2017;9(2):41-46*

Drug prescribing is among the most powerful and ubiquitous tools employed by physicians for treating patients. Over the decades, thousands of safe and effective drugs have been added to the armamentarium at physicians' disposal, empowering them to treat most of the acute and chronic conditions encountered in the community setting.

These developments, however, while generally positive, have not emerged without adding concomitant risks of harm to the patient. Administration of multiple drugs, and of herbal preparations, vitamins, and food supplements, directly increases the risk of avoidable medication error–induced sequelae, which include adverse effects, pharmacokinetic interactions, decreased efficacy, morbidity, mortality, and unnecessary resource use. Furthermore, the degree of risk is exacerbated when multiple physicians practicing various subspecialties independently prescribe medications for a patient in the absence of a case manager whose job would be to actively coordinate a cohesive care plan.

The risk of clinically significant drug-related problems (CSDRPs) is of major concern, particularly among elderly, polypharmacy-treated patients in whom the incidence of major iatrogenic events is estimated at more than 25%.[1-5] Overall, CSDRPs are responsible for approximately 2% to 5% of all hospital admissions.[6,7] Unfortunately, the growing use of electronic health record (EHR)-based modules for addressing CSDRPs has not dramatically changed the occurrences of such outcomes, given that more than 90% of physicians override or do not use these modules.[8-11] Accordingly, the development and implementation of intervention strategies, such as the requirement for pharmacists to assess drug-related problems prior to dispensing and improved uptake of existing technologies to prevent CSDRPs, is a well-established practice in managed care systems.

Although significant progress has been made in developing new technologies, the applications currently available provide suboptimal prevention of CSDRPs. Their many shortcomings include lack of systematic assessment of pharmacokinetic/pharmacogenetic data,[12] long and difficult-to-comprehend

**PRACTICAL IMPLICATIONS**

This study describes the implementation of a system that is interactively linked to a health maintenance organization's electronic health record system, which facilitates inclusion of all clinical data available to inform personalized drug-choice decisions, and the added utility this linkage provides for efficiency of patient care.

- There were 5.6% ($P$ = .001) fewer mean episodes of hospitalization, 1.5% ($P$ = .01) fewer mean drugs dispensed, and 2.1% ($P$ = .055) fewer mean episodes of imaging in the intervention population versus controls.
- Drug-related problems that were re-encountered were often rectified without re-accessing the system, indicating an educational effect among physicians who accessed the system.
- Improved physician proclivity to access the system may be attributed to its graphic presentation, comprehensiveness of relevant data, inclusion of patient-specific factors, improved specificity, and integration into the workflow of routine clinical practice.

textual outputs,[13-15] lack of suggestions for alternative drug options, an inability to evaluate drug combinations involving more than 2 concomitantly prescribed drugs, and limitation of use to the prescribing phase of the visit. Additionally, because these systems are seldom evaluated in robust controlled trials, few data are generally available to clinicians and medical managers to evaluate the potential value of these technologies in a real-life clinical setting.

A new effort to overcome many of these limitations is the Drug-Drug Interaction Plus (DDI+) decision support system (Mediseen eHealth Ltd, Teva Pharmaceutical Industries Ltd, Israel). The DDI+ output is based on a unique technology that synchronizes and integrates pharmacodynamic, pharmacokinetic, and pharmacogenetic data from leading international databases (First Data Bank and GeneMedRx/Genelex United States) along with patient-specific factors accessed from the patient's EHR in real time. The system is periodically updated with new relevant data; it incorporates innovations designed to overcome the limitations of other currently available systems to improve physician uptake and to harness the data available from EHRs to enhance the precision and specificity of CSDRP identification.

DDI+ presents real-time output via a visual user interface that enables detection, prioritization, and alternative suggestions within a few seconds while presenting only essential output to physicians throughout the entire patient office visit. DDI+ is designed to flag most of the clinically significant interactions that may occur between a drug and any other factor that may affect the pharmacokinetics/pharmacodynamics of administered medications (allergy/sensitivities, renal functions and liver function, food, vitamins, herbals, genomics, smoking, age, gender)." Additionally, in contrast to other programs limited to evaluating 2 drugs at a time, the design of DDI+ allows it to evaluate drug regimens composed of 2 or more agents to be administered concomitantly. Furthermore, DDI+ can incorporate pharmacokinetic data to prevent not only improper dosing, but also false-positive alerts that might otherwise occur when inadequately robust literature would indicate interactions. DDI+ can detect when drug-serum levels would not be affected by particular doses of 2 concomitantly prescribed drugs, despite less-specific information to the contrary in the literature.

We hypothesized that incorporating these improvements would overcome the barriers that have impeded physician use of previous systems, thereby yielding measurable improvements in the use of the following resources: hospitalization, number of drugs purchased, and imaging. The purpose of this study was to prospectively evaluate the efficacy of the DDI+ system to improve the efficiency of care in a real-world ambulatory health maintenance organization (HMO) setting via a large, robust, controlled trial.

## METHODS

### The DDI+ System

DDI+ is a Web-based system that interfaces and operates in the background of an EHR. Throughout a patient visit, the physician sees that the relevant icon on the toolbar of the EHR's main page is either "red" or "green": red signifies potential CSDRPs and green signifies their absence. When the icon is red, the physician can enter the DDI+ system either volitionally or mandatorily, depending on organizational policy. The system immediately displays the detected CSDRPs and provides information necessary to choose alternative regimens or make drug changes. Upon the physician's selection of a regimen modification or the drug to be changed, the system displays potential alternatives; it then calculates the outcomes of these (1 or more) new potential regimens, facilitating the prescription of safer alternatives. Once a CSDRP is rectified, the icon automatically switches from red to green. This platform thereby is designed to reinforce, albeit not replace, sound clinical judgment (nor does it obviate the need for independent learning).

### Patients and Setting

The DDI+ system platform was installed to interface with the EHR program used by Leumit Health Services (LHS), an HMO in Israel that provides health coverage to approximately 700,000 members with approximately

2000 physicians practicing in LHS-operated clinics or in private practice nationally. LHS first implemented its EHR system in 1999 and has achieved 100% uptake among all physicians treating LHS patients in the community setting. Complete computerization has facilitated the construction and maintenance of a data warehouse that includes comprehensive records of the following: drugs prescribed and dispensed within the system; laboratory tests ordered and their results; referrals to specialists; diagnostic imaging; hospitalizations, including scanned discharge letters; and ambulatory procedures performed at LHS clinics. Drugs prescribed outside the LHS system are not initially captured, but if a prescription is filled at an LHS-affiliated pharmacy or if the drug is later re-prescribed by an LHS physician, the system will document the prescription. Furthermore, LHS has developed and implemented data-capture and analysis tools for the EHR data warehouse that enable both longitudinal and retrospective observation of resource use in its defined patient and physician populations.

All elderly patients (≥65 years) receiving polypharmacy (≥5 concomitant chronic medications) were included for healthcare use assessments. Access rates and the system's educational capacities were evaluated only for primary care physicians who treated these elderly patients (n = 369 and n = 346 for the intervention and control arms, respectively) as they were the main target population of the DDI+ system from the LHS perspective.

### Study Design, Data Accrual, and Outcome Variables

The LHS management structure is subdivided into 4 geographic regions subordinate to a central management. Physicians were geographically allocated by region where they practice to a study arm that received access to the DDI+ platform (North and Central regions) or a control arm that was not (Jerusalem and South regions). Because the North and South regions and the Central and Jerusalem regions are similar in patient and physician demographics, the 4 regions were accordingly allocated into 2 groups. The allocation of these 2 groups into study and control arms was arbitrary. We chose to implement the system on regions in their entirety and not to randomize individual physicians in order to prevent cross-group contamination among physicians in different arms of the study working in the same region. Neither arm was exposed to other decision-support technologies. After a run-in period that included an individual 30-minute training program, the system was formally launched in the study arm of physicians on January 1, 2013, for a 6-month controlled study period. Use of the program was voluntary, and physician access patterns during the study were not monitored to promote use among physicians who declined to do so.

Data were accrued and compared for both groups. To evaluate the efficacy of the system to reduce resource use, we calculated and compared the average number of episodes of hospitalization and imaging and the number of drugs dispensed per patient in both arms during the study period with those observed in these patients during the 12-month preintervention period. We then calculated the relative changes observed between the pre- and postintervention periods. The rationale for analyzing the use of imaging was that because a physician may not immediately identify a primary complaint as a CSDRP, these patients are frequently referred to diagnostic procedures, such as imaging, to rule out suspected pathologies included in the differential diagnosis. The effectiveness of the system to rectify alerted problematic drug combinations was measured by calculating the percentage of red alerts that turned green among patients treated by physicians who accessed the system compared with the rate observed among patients treated by physicians in the intervention arm who did not access the system.

Additionally, the change in number of "severe" alerts present among patients treated by DDI+ users was calculated longitudinally over the 6-month study period. Changes in drug utilization patterns after an alert was rectified were measured by calculating the average number of drugs dispensed to patients before and after the first time a red alert turned green. Additionally, we evaluated physician acceptance and application of the system by measuring both crude physician use rates (rates of physicians accessing the system at least once) and the proportion of alerted episodes in which the physician accessed the system. Furthermore, because we postulated that the system might yield a residual educational effect, we identified and quantified episodes of drug switching without accessing the system following an episode involving the same clinical scenario in which the physician heeded the alert.

Data capture was performed using IBM Cognos 10.1.1 BI Report Studio software (IBM, Armonk, New York). Results of queries were downloaded into Microsoft Excel (version 14) spreadsheets for statistical analysis. Student's *t* test, $\chi^2$ test, and 1-way analysis of variance were used as appropriate. All results are expressed as average ± standard deviation, percent with *P* value, or 95% confidence interval. A *P* value ≤.05 was considered statistically significant. The data were analyzed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

The study was approved by LHS's Institutional Review Board and was registered (ClinicalTrials.gov identifier: NCT 01765595).

**Table 1.** Characteristics of Patient and Physician Populations

| | Intervention Group | Control Group | *P* |
|---|---|---|---|
| Patient Characteristics | N = 18,920 | N = 14,023 | |
| Age, years (mean ± SD) | 76.4 ± 7.4 | 76.4 ± 7.3 | .941[a] |
| Gender (% male) | 40 | 40 | .952[b] |
| Number of distinct drug products received during year prior to study period (mean ± SD) | 8.0 ± 3.13 | 7.9 ± 3.1 | .103[a] |
| Primary care physician visits during year prior to study period (mean ± SD) | 4.3 ± 3.5 | 4.2 ± 3.4 | <.001[a] |
| Physician Characteristics | N = 369 | N = 346 | |
| Age, years (mean ± SD) | 52.7 ± 9.8 | 52.9 ± 9.2 | .758[a] |
| Gender (% male) | 68 | 61 | <.05[b] |
| Number of distinct patients treated during study period (mean ± SD)[c] | 1213 ± 911 | 1333 ± 1147 | .122[a] |
| Aggregate number of patient visits during study period (mean ± SD)[c] | 3391 ± 2687 | 3208 ± 2873 | .379[a] |

SD indicates standard deviation.
[a]*P* value calculated by *t* test.
[b]*P* value calculated by $\chi^2$ test.
[c]Including patients not in the study.

## RESULTS

The characteristics of the intervention and control populations of patients and physicians appear in **TABLE 1**. Differences in physician gender and average number of primary care physician visits during the year prior to the study period were found to be statistically but not clinically significant. Statistically significant variance between the 2 groups was not observed in the other variables measured, including the number of distinct drug products received during the year prior to the study period, a proxy variable for number of comorbidities and disease severity.

The changes in resource use in the intervention and control arms (difference-in-differences methodology) appear in **TABLE 2**. Although a rise in utilization of resources was observed in both groups, there were 5.6% ($P = .001$) fewer mean episodes of hospitalization, 1.5% ($P = .01$) fewer mean drugs dispensed, and 2.1% ($P = .055$) fewer mean episodes of imaging in the intervention population versus controls.

A subset analysis of the primary physicians in the intervention arm who accessed the system was conducted. During the 6-month study period, 272 of the 369 primary physicians (78.6%) accessed the system at least once. At least 1 episode of a "red alert" was documented during 104,711 visits. Physician voluntary access rates during these visits was observed to be 12.9% (n = 13,534). A red alert was observed to be converted to green during 5386 (39.8%) of these 13,534 visits, versus 0.6% ($P < .0001$) among physicians who did not access the system despite having been exposed to the red-alert icon (**TABLE 3**). Among the 272 physicians who accessed the system at least once, 232 (85.3%; 95% CI, 80.5%-89.3%) were observed to appropriately respond to later alerts without subsequently accessing the system, correctly rectifying 68.9% of the potential CSDRPs re-encountered. At the conclusion of the 6-month study period, 42% of the initial "severe" alerts had been resolved by the physicians in the intervention arm who accessed DDI+ at least once ($P = .023$) (**FIGURE**). Additionally, the average number of drugs dispensed to a patient after a red alert was resolved decreased by 7.8%, from 9.77 ± 3.62 to 9.01 ± 2.93 medications per patient ($P < .05$).

## DISCUSSION

The observed success of this program compared with other marketed systems can be attributed to the unique features incorporated into the system to overcome the shortcomings of previous efforts. First, and most significant, the DDI+ system is interactively linked to the HMO's EHR

**Table 2.** Resource Utilization Patterns Before and After Intervention

| | Intervention Group | | | Control Group | | | | |
|---|---|---|---|---|---|---|---|---|
| Resource | 2012 | 2013 | % Change 2013-2012 | 2012 | 2013 | % Change 2013-2012 | Change[b] (intervention vs control) | *P*[c] |
| Hospitalization (mean number of episodes/patient) | 0.21 | 0.26 | 22.8 | 0.173 | 0.2222 | 28.4 | -5.6 | .001 |
| Medication (mean number of drugs purchased) | 72.25 | 72.75 | 0.7 | 71.7253 | 73.3365 | 2.2 | -1.5 | .0102 |
| Imaging[a] (mean number of episodes/patient) | 0.78 | 0.74 | -5.0 | 0.7168 | 0.6962 | -2.9 | -2.1 | .0551 |

[a]Ultrasound, magnetic resonance imaging, computed tomography.
[b]Calculated as the difference in the percent change measured over the years 2013 and 2012 between the intervention group and the control group.
[c]*P* value by analysis of variance for differences between groups.



system, which facilitates inclusion of all clinical data available to inform personalized drug choice decisions. We understand that this feature generates confidence among physicians concerning the relevance of the alternatives, thereby allaying previously observed apprehensions caused by the low specificity (eg, frequent false-positive alerts) that characterized other systems,

**Table 3.** Rates of Resolved Alerts Among Patients in Study Arm, Stratified by Physician DDI+ Users and Nonusers

| | DDI+ Users (n = 272) | | DDI+ Nonusers (n = 74) | | *P*[a] |
|---|---|---|---|---|---|
| Alerted interactions ("red") that turned to nonalerted ("green") | 5386 | 39.8% | 52 | 0.6% | |
| Unchanged alerted ("red") interactions | 8148 | 60.2% | 9035 | 99.4% | <.0001 |
| Total number of alerted interactions ("red" icons) | 13,534 | 100% | 9087 | 100% | |

DDI+ indicates Drug-Drug Interaction Plus decision support system.
[a]By $\chi^2$ test.

Second, in contrast to other programs, the DDI+ system processes the "net" outcome of drug combinations of more than 2 medications administered concomitantly. This unique feature may have afforded an elevated perception of reliability among physicians equipped with the system. Third, significant efforts were made to provide the physician with a user-friendly visual interface that enables a favorable workflow, one that streamlines integration of the system into routine care without disrupting the dynamics of the office visit. Accordingly, the system facilitated rapid detection, prioritization, and complex problem solving. Moreover, because the "red alert" was visible even without accessing the system, it is possible that this notification was sufficient to motivate physicians to resolve the warning without the aid of the system. Fourth, in contrast to other systems that flag only potential severe interactions, the DDI+ system is designed to provide information to guide clinical decision processes for prescription of safer, alternative drug regimens. Additionally, although not measured, it is possible that presenting only essential output to physicians diminished alert fatigue, thereby improving motivation to access the system.[11] Finally, the superior access rates observed may be attributable to the opportunity the system gives to physicians to access the system at all stages of the office visit, not just during the prescription phase.

The findings of this study indicate that integration of the DDI+ system into the EHR used during routine practice may yield measurable improvements in resource use. The change in aggregate utilization measured for hospitalization, medication, and imaging, compared with the preintervention period, was found to rise to a lesser degree in the intervention arm compared with controls. These findings may indicate that the system was successful in attenuating portions of the drug-induced morbidity responsible for the rise in healthcare expenditures. Furthermore, these findings suggest that organizations installing the DDI+ program should implement a program for monitoring access rates to promote use among physicians who opt not to do so.

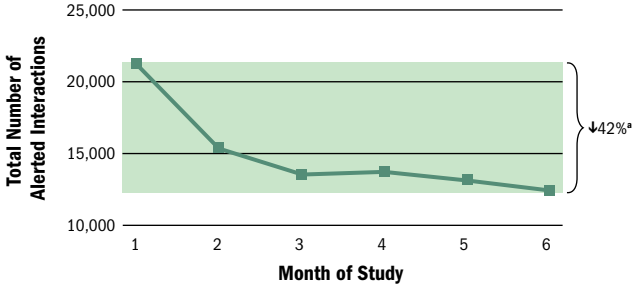
It is possible that the accessing physicians may have been a selected subgroup of physicians particularly interested in rational and safe use of medications, and the improved outcomes and utilization patterns (eg, reduction of number of medications per patient) could reflect a more rational medical care provided by this subgroup of physicians rather than being the result of the clinical decision support system.

Of particular interest is the observed educational effect among physicians who accessed the system. The implication of this finding is that the DDI+ system is inherently a continuing medical education (CME) tool for conveying information on CSDRPs during primary care visits. This finding is significant, as it introduces a new paradigm in CME whereby physicians receive information pertinent to the medications they routinely prescribe while attending to their patients. The graphic presentation was probably contributory to this observed behavior. Accordingly, the utility of the system as a CME tool is further augmented through systematic updating of the root databases of interactions, thereby assuring that new information is presented to practicing physicians as available.

## Strengths and Limitations

To our knowledge, this study is the first large real-world controlled trial of a computerized CSDRP alert system to be conducted nationally in a managed care setting. This study has number of strengths. First, this trial included

**Figure.** Change in Total Number of Alerts in the Study Arm Over the Study Period




[a]*P* = .023. By *P* for trend in linear regression.

the entire physician population of a large HMO, thus obviating the need for sampling for either the intervention or control arms. Potential biases caused by sampling errors were thereby avoided. Additionally, because the program interfaced with LHS's EHR system, all data necessary to longitudinally evaluate resource use in both arms of the study were available.

The limitations include: 1) not randomizing physicians into the 2 study arms, and 2) potential bias caused by selective physician access rates and patterns. Unfortunately, we were unable to capture sufficient data to explore physician traits that may have been determinants in proclivity to access the system, and we were unable to account for unmeasured exogenous factors that may have contributed to the decreases in resource use we observed. Similarly, because the system was not implemented in the background of the control arm, we were unable to monitor incidence of alerts that would have appeared among these physicians for comparison with the study arm. Conversely, however, regional, as opposed to random, allocation may have provided a more robust methodology as it preempted potential cross-group contamination among physicians in different arms of the study working in the same region. Finally, although the system was found to improve efficiency in this study, we recognize that this analysis was limited to 1 HMO; therefore, these findings may not be completely generalizable to other healthcare settings.

## CONCLUSIONS

The DDI+ system was observed to be better accepted than other similar systems (according to reported data) among physicians. We surmise that improved physician willingness to access the DDI+ system can be attributed to its graphic presentation, comprehensiveness of relevant data, inclusion of patient-specific factors, improved specificity, and integration into the workflow of routine clinical practice. This improvement in physician proclivity to access and utilize the system may have resulted in improvements in resource-utilization patterns in treating patients. ajpb

***Author Affiliations:*** Medical Division, Leumit Health Services (NRK, D-AW), Tel Aviv, Israel; School of Public Health (NRK), and Sackler Faculty of Medicine (NRK, MB, AW), and Faculty of Management (JG), Tel Aviv University, Tel Aviv, Israel; Asaf Harofe Medical Center (MB), Tsrifin, Israel; School of Pharmacy, The Hebrew University of Jerusalem (SYS), Israel; Geha Mental Health Center (AW), Petach Tikva, Israel; Teva Pharmaceutical Industries, Ltd (RS), Petach Tikva, Israel; University of Warwick (JG), Coventry, UK.

***Source of Funding:*** This study was partially funded by Teva Pharmaceuticals and by GeneMedRx.

***Author Disclosures:*** Drs Superstine and Weizman have received consulting fees from Teva Pharmaceutical Industries, Ltd. Dr Shiloh is an employee of Teva Pharmaceutical Industries, Ltd. The remaining authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

***Authorship Information:*** Concept and design (NRK, D-AW, MB, SYS, JG, AW, RS); acquisition of data (NRK, D-AW, MB, RS); analysis and interpretation of data (NRK, D-AW, MB, SYS, JG, AW); drafting of the manuscript (NRK, D-AW, MB, AW, RS); critical revision of the manuscript for important intellectual content (NRK, D-AW, MB, SYS, JG, AW, RS); obtaining funding (RS); administrative, technical, or logistic support (D-AW, RS); and supervision (D-AW, RS).

***Address Correspondence to:*** Natan R. Kahan, PhD, RPh, MHA, Leumit Health Services, 23 Schprintsak St, Tel Aviv, Israel 64738. E-mail: nkahan@leumit.co.il.

## REFERENCES

1. Ahmad A, Mast MR, Nijpels G, Elders PH, Dekker JM, Hugtenburg JG. Identification of drug-related problems of elderly patients discharged from hospital. *Patient Prefer Adherence*. 2014;8:155-165. doi: 10.2147/PPA.S48357.
2. Hohl CM, Dankoff J, Colacone A, Afilalo M. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. *Ann Emerg Med*. 2001;38(6):666-671.
3. Tulner LR, Frankfort SV, Gijsen GJ, van Campen JP, Koks CH, Beijnen JH. Drug-drug interactions in a geriatric outpatient cohort: prevalence and relevance. *Drugs Aging*. 2008;25(4):343-355.
4. Doucet J, Chasssagne P, Trivalle C, et al. Drug-drug interactions related to hospital admissions in older adults: a prospective study of 1000 patients. *J Am Geriatr Soc*. 1996;44(8):944-948.
5. Lindley CM, Tully MP, Paramsothy V, Tallis RC. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. *Age Ageing*. 1992;21(4):294-300.
6. Jankel CA, Fitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. *Drug Saf*. 1993;9(1):51-59.
7. Hamilton RA, Briceland LL, Andritz MH. Frequency of hospitalization after exposure to known drug-drug interactions in a Medicaid population. *Pharmacotherapy*. 1998;18(5):1112-1120.
8. Yeh ML, Chang YJ, Wang PY, Li YC, Hsu CY. Physicians' responses to computerized drug-drug interaction alerts for outpatients. *Comput Methods Programs Biomed*. 2013;111(1):17-25. doi: 10.1016/j.cmpb.2013.02.006.
9. Van der Sijs H, Mulder A, van Gelder T, Aarts J, Berg M, Vulto A. Drug safety alert generation and overriding in a large Dutch university medical centre. *Pharmacoepidemol Drug Saf*. 2009;18(10):941-947. doi: 10.1002/pds.1800.
10. Beeler PE, Eschmann E, Rosen C, Blaser J. Use of an on-demand drug-drug interaction checker by prescribers and consultants: a retrospective analysis in a Swiss teaching hospital. *Drug Saf*. 2013;36(6):427-434. doi: 10.1007/s40264-013-0022-1.
11. Phansalkar S, van der Sijs H, Tucker AD, et al. Drug-drug interactions that should be non-interruptive in order to reduce alert fatigue in electronic health records. *J Am Med Inform Assoc*. 2013;20(3):489-493.
12. Doan J, Zakrzewski-Jakubiak H, Roy J, Turgeon J, Tannenbaum C. Prevalence and risk of potential cytochrome P450-mediated drug-drug interactions in older hospitalized patients with polypharmacy. *Ann Pharmacother*. 2013;47(3):324-332. doi: 10.1345/aph.1R621.
13. Miller GA. The magical number seven, plus or minus two: some limits on our capacity for processing information. *Psychol Rev*. 1956;63(2):81-97.
14. Cowan N. The magical number 4 in short-term memory: a reconsideration of mental storage capacity. *Behav Brain Sci*. 2001;24(1):87-114.
15. Broadbent DE. The magic number seven after fifteen years. In: Kennedy A, Wilkes A, ed. *Studies in Long Term Memory*. London, England: John Wiley & Sons; 1975: 3-15.