Digital Personalized Health and Medicine
L.B. Pape-Haugaard et al. (Eds.)

doi:10.3233/SHTI200247

Statistically Prioritized and Contextualized Clinical Decision Support Systems, the Future of Adverse Drug Events Prevention?

Emmanuel CHAZARD[a,1], Jean-Baptiste BEUSCART[a], Michaël ROCHOY[b], Olivia DALLEUR[c], Bertrand DECAUDIN[d], Pascal ODOU[d], and Grégoire FICHEUR[a]
[a] *Univ. Lille, CHU Lille, CERIM EA2694, F-59000 Lille, France*
[b] *Univ. Lille, CERIM EA2694, General practitioner, F-59000 Lille, France*
[c] *Pharmacy Department, Université catholique de Louvain, 1200, Brussels, Belgium.*
[d] *Univ. Lille, CHU Lille, EA7365 GRITA, F-59000 Lille, France*

Abstract. Clinical decision support systems (CDSS) fail to prevent adverse drug events (ADE), notably due to over-alerting and alert-fatigue. Many methods have been proposed in the literature to reduce over-alerting of CDSS: enhancing post-alert medical management, taking into account user-related context, patient-related context and temporal aspects, improving medical relevance of alerts, filtering or tiering alerts on the basis of their strength of evidence, their severity, their override rate, or the probability of outcome. This paper analyzes the different options, and proposes the setup of SPC-CDSS (statistically prioritized and contextualized CDSS). The principle is that, when a SPC-CDSS is implemented in a medical unit, it first reuses actual clinical data, and searches for traceable outcomes. Then, for each rule trying to prevent this outcome, the SPC-CDSS automatically estimates the conditional probability of outcome knowing that the conditions of the rule are met, by retrospective secondary use of data. The alert can be turned off below a chosen probability threshold. This probability computation can be performed in each medical unit, in order to take into account its sensitivity to context.

Keywords. Adverse drug events, Clinical decision support systems, data reuse.

1. Introduction

Adverse drug events (ADEs) are the most common type of iatrogenic injury. It is commonly admitted that coupling a clinical decision support system (CDSS) with a computerized order entry system (CPOE) may prevent ADEs [1]. But for current CDSS, over-alerting is an important issue: too numerous and inappropriate alerts may interrupt the clinicians' workflow and induce alert-fatigue [2,3], anger or annoyance [4]. This may prevent CDSS from improving patient safety [3,5]. As a consequence, up to 96% of alerts are overridden by prescribers [2,6–10], mainly because of poor appropriateness [11,12]. Unfortunately, appropriate alerts may be perceived as useless [2] and then overridden, but followed by actual ADEs [13–16]. The objective of this work is to propose a new approach to improve the ability of CDSS to prevent ADEs.

[1] Corresponding Author: emmanuel.chazard@univ-lille.fr

2. Material and methods

We first performed a narrative review of the tracks that have been proposed in the scientific literature, to reduce the over-alerting and alert-fatigue of CDSS, by searching for scientific papers in the Medline database, without time limit (keywords: CDSS, alert-fatigue, over-alerting). We also performed a recursive search including papers cited by those papers, and additional keywords. We then classified and discussed the tracks exposed in those papers. We finally proposed a new approach named SPC-CDSS (see below), in accordance with the results.

3. Results

3.1. Narrative review

In order to decrease over-alerting and alert-fatigue, it has been proposed to improve the way the CDSS interacts with the prescriber, and notably to improve the way the alerts are displayed [4], to provide the users with relevant instructions for post-alert medical management [3,17–19], and to involve non-medical healthcare professionals [6]. Some works also proposed to take into account the context of the drug prescription: user-related context (task, workflow, knowledge, preferences, medical unit) [2,20–22] and patient-related context (demographic data, risk factors) [3,17,20,21]. The temporal aspects have been identified as an important aspect: half of the prescribing errors occur on the first day of stay [14], the repetition of alerts has to be handled [9,20,21,23], as well as the kinetic of laboratory parameters [24].

It has also been proposed to improve the medical relevance of rules. One important track is to filter or tier the alerts by taking into account the strength of evidence [3,20,21]. It has been also proposed to ask medical experts to tier the alerts function of the severity of the potential outcome [3,5,6,20,21,25–27]: this approach seems to bring good results [5,25,27], but the experts hardly agree on the way to classify the rules [5,28]. Another option is to turn off rules that have the highest override rates [5,20,21,29]: this is efficient and mechanically decreases the override rate [29], but other studies demonstrated that most alert overrides were inappropriate [13–16].

Finally, given an ADE prevention rule, the conditional probability of ADE knowing that the conditions of the rule are met could be used to turn a rule on or off. This feature is largely asked by the physicians [3,20,21]. However, those approaches are still not implemented, although the reuse of electronic health records could enable to automatically estimate the conditional empirical probabilities of ADEs [30–33].

3.2. Proposal of SPC-CDSS

We propose to implement SPC-CDSS, which stands for “Statistically prioritized and contextualized clinical decision support systems”. The main idea is that, when a SPC-CDSS is implemented in a medical unit, it first reuses actual clinical data, and automatically searches for traceable outcomes (e.g. “INR>5”). Then, for each rule trying to prevent this outcome (e.g. “vitamin K antagonist & quinolone → risk of increased INR”), the SPC-CDSS automatically estimates the conditional probability of outcome, knowing that the conditions of the rule are met. In case of low probability

(the threshold can be customized), the corresponding alerts are automatically turned off ("statistically prioritized"). Moreover, this computation is performed in each medical unit, in order to take into account its sensitivity to context ("statistically contextualized"). This notion of context is a statistical proxy for latent undocumented variables, such as patients' characteristics (e.g. some conditions, admission ground), organizational characteristics (e.g. monitoring policies), and physicians' characteristics (e.g. knowledge about drugs, specialty, risk aversion) [30].

4. Discussion

Being able to compute the empirical probability of outcome for each ADE prevention rule may allow for two main benefits, that have been tested [30,33,34]. The first benefit could be to turn off some rules which empirical probability is below a chosen threshold ("A" arrow on Figure 1). Many CDSS rules are inappropriate [11,12], but experts hardly agree on which rule should be turned off [5,28]. The second benefit could be to show empirical evidence to the physicians to improve their adherence to the remaining alerts ("B" arrow on Figure 1). Indeed, too many appropriate rules are overridden by users [13–16]. Moreover, such information is requested by many physicians [3,20,21].

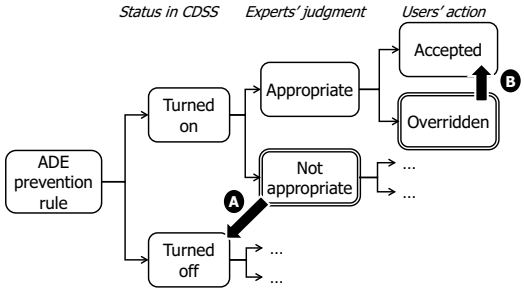

Figure 1. Expected benefits of SPC-CDSS: (A) turning some rules off, and (B) making rules more acceptable

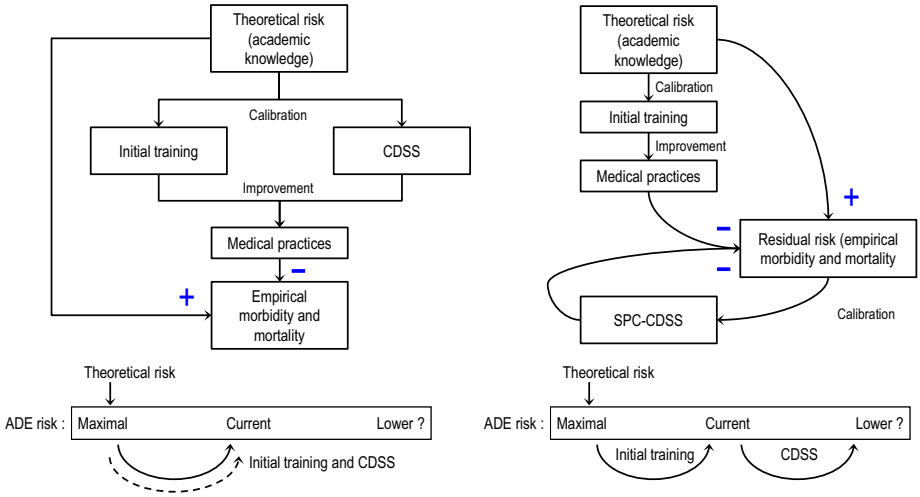

Figure 2. Left: current paradigm for ADE prevention. Right: proposed paradigm for ADE prevention.

The current paradigm for ADE prevention relies on the idea that CDSS should be calibrated based on the current academic knowledge (left part of Figure 2). But the physicians have also been initially trained on the basis of this knowledge. Consequently, the CDSS alerts are redundant with their own knowledge, and are useless. We propose to consider that the empirical morbidity and mortality are a residual risk, i.e. the maximal theoretical risk minus the benefits of the physicians' training. We then propose (right part of Figure 2) to use those empirical probabilities to calibrate the SPC-CDSS. Then, the SPC-CDSS alerts would be able to handle situations that have not been properly prevented by the initial training of the physicians. In terms of ADE risk, these considerations are summarized at the bottom of Figure 2.

The present proposal should be tested and evaluated using actual clinical data. It also rises new issues, such as the threshold to choose, the variability between physicians, and the medical staff turnover. Finally, other solutions may be proposed to consider the final user's point of view.

References

[1] A.X. Garg, N.K.J. Adhikari, H. McDonald, M.P. Rosas-Arellano, P.J. Devereaux, J. Beyene, J. Sam, and R.B. Haynes, Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review, *JAMA J. Am. Med. Assoc.* **293** (2005) 1223–1238. doi:10.1001/jama.293.10.1223.

[2] H. van der Sijs, J. Aarts, A. Vulto, and M. Berg, Overriding of drug safety alerts in computerized physician order entry, *J. Am. Med. Inform. Assoc. JAMIA*. **13** (2006) 138–147. doi:10.1197/jamia.M1809.

[3] S. Phansalkar, A. Desai, A. Choksi, E. Yoshida, J. Doole, M. Czochanski, A.D. Tucker, B. Middleton, D. Bell, and D.W. Bates, Criteria for assessing high-priority drug-drug interactions for clinical decision support in electronic health records, *BMC Med. Inform. Decis. Mak.* **13** (2013) 65. doi:10.1186/1472-6947-13-65.

[4] M. Jung, A. Hoerbst, W.O. Hackl, F. Kirrane, D. Borbolla, M.W. Jaspers, M. Oertle, V. Koutkias, L. Ferret, P. Massari, K. Lawton, D. Riedmann, S. Darmoni, N. Maglaveras, C. Lovis, and E. Ammenwerth, Attitude of physicians towards automatic alerting in computerized physician order entry systems. A comparative international survey, *Methods Inf. Med.* **52** (2013) 99–108. doi:10.3414/ME12-02-0007.

[5] H. van der Sijs, J. Aarts, T. van Gelder, M. Berg, and A. Vulto, Turning off frequently overridden drug alerts: limited opportunities for doing it safely, *J. Am. Med. Inform. Assoc. JAMIA*. **15** (2008) 439–448. doi:10.1197/jamia.M2311.

[6] P.L. Smithburger, M.S. Buckley, S. Bejian, K. Burenheide, and S.L. Kane-Gill, A critical evaluation of clinical decision support for the detection of drug-drug interactions, *Expert Opin. Drug Saf.* **10** (2011) 871–882. doi:10.1517/14740338.2011.583916.

[7] H. van der Sijs, A. Mulder, T. van Gelder, J. Aarts, M. Berg, and A. Vulto, Drug safety alert generation and overriding in a large Dutch university medical centre, *Pharmacoepidemiol. Drug Saf.* **18** (2009) 941–947. doi:10.1002/pds.1800.

[8] C.-P. Lin, T.H. Payne, W.P. Nichol, P.J. Hoey, C.L. Anderson, and J.H. Gennari, Evaluating clinical decision support systems: monitoring CPOE order check override rates in the Department of Veterans Affairs' Computerized Patient Record System, *J. Am. Med. Inform. Assoc. JAMIA*. **15** (2008) 620–626. doi:10.1197/jamia.M2453.

[9] T. Isaac, J.S. Weissman, R.B. Davis, M. Massagli, A. Cyrulik, D.Z. Sands, and S.N. Weingart, Overrides of medication alerts in ambulatory care, *Arch. Intern. Med.* **169** (2009) 305–311. doi:10.1001/archinternmed.2008.551.

[10] M.-L. Yeh, Y.-J. Chang, P.-Y. Wang, Y.-C.J. Li, and C.-Y. Hsu, Physicians' responses to computerized drug-drug interaction alerts for outpatients, *Comput. Methods Programs Biomed.* **111** (2013) 17–25. doi:10.1016/j.cmpb.2013.02.006.

[11] A.B. Taegtmeyer, G.A. Kullak-Ublick, N. Widmer, V. Falk, and A. Jetter, Clinical usefulness of electronic drug-drug interaction checking in the care of cardiovascular surgery inpatients, *Cardiology*. **123** (2012) 219–222. doi:10.1159/000343272.

[12] D. Fritz, A. Ceschi, I. Curkovic, M. Huber, M. Egbring, G.A. Kullak-Ublick, and S. Russmann, Comparative evaluation of three clinical decision support systems: prospective screening for medication errors in 100 medical inpatients, *Eur. J. Clin. Pharmacol.* **68** (2012) 1209–1219. doi:10.1007/s00228-012-1241-6.

[13] S.P. Slight, D.L. Seger, K.C. Nanji, I. Cho, N. Maniam, P.C. Dykes, and D.W. Bates, Are we heeding the warning signs? Examining providers' overrides of computerized drug-drug interaction alerts in primary care, *PloS One*. **8** (2013) e85071. doi:10.1371/journal.pone.0085071.

[14] T. Caruba, I. Colombet, F. Gillaizeau, V. Bruni, V. Korb, P. Prognon, D. Bégué, P. Durieux, and B. Sabatier, Chronology of prescribing error during the hospital stay and prediction of pharmacist's alerts overriding: a prospective analysis, *BMC Health Serv. Res.* **10** (2010) 13. doi:10.1186/1472-6963-10-13.

[15] K.C. Nanji, S.P. Slight, D.L. Seger, I. Cho, J.M. Fiskio, L.M. Redden, L.A. Volk, and D.W. Bates, Overrides of medication-related clinical decision support alerts in outpatients, *J. Am. Med. Inform. Assoc. JAMIA*. **21** (2014) 487–491. doi:10.1136/amiajnl-2013-001813.

[16] H. van der Sijs, T. van Gelder, A. Vulto, M. Berg, and J. Aarts, Understanding handling of drug safety alerts: a simulation study, *Int. J. Med. Inf.* **79** (2010) 361–369. doi:10.1016/j.ijmedinf.2010.01.008.

[17] J.D. Duke, and D. Bolchini, A successful model and visual design for creating context-aware drug-drug interaction alerts, *AMIA Annu. Symp. Proc. AMIA Symp. AMIA Symp.* **2011** (2011) 339–348.

[18] A. Floor-Schreudering, P.A.G.M. De Smet, H. Buurma, S. Amini, and M.L. Bouvy, Clarity and applicability of drug-drug interaction management guidelines: a systematic appraisal by general practitioners and community pharmacists in the Netherlands, *Drug Saf. Int. J. Med. Toxicol. Drug Exp.* **34** (2011) 683–690. doi:10.2165/11587270-000000000-00000.

[19] J.D. Duke, X. Li, and P. Dexter, Adherence to drug-drug interaction alerts in high-risk patients: a trial of context-enhanced alerting, *J. Am. Med. Inform. Assoc. JAMIA*. **20** (2013) 494–498. doi:10.1136/amiajnl-2012-001073.

[20] E. Ammenwerth, W.O. Hackl, D. Riedmann, and M. Jung, Contextualization of automatic alerts during electronic prescription: researchers' and users' opinions on useful context factors, *Stud. Health Technol. Inform.* **169** (2011) 920–924.

[21] D. Riedmann, M. Jung, W.O. Hackl, W. Stühlinger, H. van der Sijs, and E. Ammenwerth, Development of a context model to prioritize drug safety alerts in CPOE systems, *BMC Med. Inform. Decis. Mak.* **11** (2011) 35. doi:10.1186/1472-6947-11-35.

[22] R. Marcilly, N. Leroy, M. Luyckx, S. Pelayo, C. Riccioli, and M.-C. Beuscart-Zéphir, Medication related computerized decision support system (CDSS): make it a clinicians' partner!, *Stud. Health Technol. Inform.* **166** (2011) 84–94.

[23] G.J. Kuperman, A. Bobb, T.H. Payne, A.J. Avery, T.K. Gandhi, G. Burns, D.C. Classen, and D.W. Bates, Medication-related Clinical Decision Support in Computerized Provider Order Entry Systems: A Review, *J. Am. Med. Inform. Assoc.* **14** (2007) 29–40. doi:10.1197/jamia.M2170.

[24] E. Eschmann, P.E. Beeler, G. Zünd, and J. Blaser, Evaluation of alerts for potassium-increasing drug-drug-interactions, *Stud. Health Technol. Inform.* **192** (2013) 1056.

[25] M.D. Paterno, S.M. Maviglia, P.N. Gorman, D.L. Seger, E. Yoshida, A.C. Seger, D.W. Bates, and T.K. Gandhi, Tiering drug-drug interaction alerts by severity increases compliance rates, *J. Am. Med. Inform. Assoc. JAMIA*. **16** (2009) 40–46. doi:10.1197/jamia.M2808.

[26] S. Phansalkar, H. van der Sijs, A.D. Tucker, A.A. Desai, D.S. Bell, J.M. Teich, B. Middleton, and D.W. Bates, Drug-drug interactions that should be non-interruptive in order to reduce alert fatigue in electronic health records, *J. Am. Med. Inform. Assoc. JAMIA*. **20** (2013) 489–493. doi:10.1136/amiajnl-2012-001089.

[27] N.R. Shah, A.C. Seger, D.L. Seger, J.M. Fiskio, G.J. Kuperman, B. Blumenfeld, E.G. Recklet, D.W. Bates, and T.K. Gandhi, Improving override rates for computerized prescribing alerts in ambulatory care, *AMIA Annu. Symp. Proc. AMIA Symp. AMIA Symp.* (2005) 1110.

[28] H.R. Strasberg, A. Chan, and S.J. Sklar, Inter-rater agreement among physicians on the clinical significance of drug-drug interactions, *AMIA Annu. Symp. Proc. AMIA Symp. AMIA Symp.* **2013** (2013) 1325–1328.

[29] E.K. Lee, A.F. Mejia, T. Senior, and J. Jose, Improving Patient Safety through Medical Alert Management: An Automated Decision Tool to Reduce Alert Fatigue, *AMIA Annu. Symp. Proc. AMIA Symp. AMIA Symp.* **2010** (2010) 417–421.

[30] E. Chazard, S. Bernonville, G. Ficheur, and R. Beuscart, A statistics-based approach of contextualization for adverse drug events detection and prevention, *Stud. Health Technol. Inform.* **180** (2012) 766–770.

[31] E. Eschmann, P.E. Beeler, V. Kaplan, M. Schneemann, G. Zünd, and J. Blaser, Clinical decision support for monitoring drug-drug-interactions and potassium-increasing drug combinations: need for specific alerts, *Stud. Health Technol. Inform.* **180** (2012) 1200–1202.

[32] A.M. Miller, M.S. Boro, N.E. Korman, and J.B. Davoren, Provider and pharmacist responses to warfarin drug-drug interaction alerts: a study of healthcare downstream of CPOE alerts, *J. Am. Med. Inform. Assoc. JAMIA*. **18 Suppl 1** (2011) i45-50. doi:10.1136/amiajnl-2011-000262.

[33] E. Chazard, G. Ficheur, S. Bernonville, M. Luyckx, and R. Beuscart, Data mining to generate adverse drug events detection rules, *IEEE Trans. Inf. Technol. Biomed. Publ. IEEE Eng. Med. Biol. Soc.* **15** (2011) 823–830. doi:10.1109/TITB.2011.2165727.

[34] V. Koutkias, V. Kilintzis, G. Stalidis, K. Lazou, C. Collyda, E. Chazard, P. McNair, R. Beuscart, and N. Maglaveras, Constructing Clinical Decision Support Systems for Adverse Drug Event Prevention: A Knowledge-based Approach, *AMIA Annu. Symp. Proc. AMIA Symp. AMIA Symp.* **2010** (2010) 402–406.