

Original Article

A comparison of five common drug–drug interaction software programs regarding accuracy and comprehensiveness

Raziyeh Kheshti¹, Mohammadsadegh Aalipour¹, Soha Namazi¹

¹Department of Clinical Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

Objective: Drug–drug interactions (DDIs) can cause failure in treatment and adverse events. DDIs screening software is an important tool to aid clinicians in the detection and management of DDIs. However, clinicians should be aware of the advantages and limitations of these programs. We compared the ability of five common DDI programs to detect clinically important DDIs.

Methods: Lexi-Interact, Micromedex Drug Interactions, iFacts, Medscape, and Epocrates were evaluated. The programs' sensitivity, specificity, and positive and negative predictive values were determined to assess their accuracy in detecting DDIs. The accuracy of each program was identified using 360 unknown pair interactions, taken randomly from prescriptions, and forty pairs of clinically important ones. The major reference was a clinical pharmacist alongside the Stockley's Drug Interaction and databases including PubMed, Scopus, and Google Scholar. Comprehensiveness of each program was determined by the number of components in the drug interaction monograph. The aggregate score for accuracy and comprehensiveness was calculated.

Findings: Scoring 250 out of possible 400 points, Lexi-Interact and Epocrates, provided the most accurate software programs. Micromedex, Medscape, and iFacts ranked third, fourth, and fifth, scoring 236, 202, and 191, respectively. In comprehensiveness test, iFacts showed the highest score, 134 out of possible 134 points, whereas Lexi-Interact rated second, with a score of 120. Scoring 370 and 330 out of possible 534 points, Lexi-Interact and Micromedex, respectively, provided the most competent, complete, and user-friendly applications.

Conclusion: Lexi-Interact and Micromedex showed the best performances. An increase in sensitivity is possible by the combination of more than one programs and expert pharmacist intervention.

Keywords: Accuracy; comprehensiveness; drug interaction screening program; drug–drug interactions software

Received: May 2016
Accepted: August 2016

Corresponding author:
Dr. Soha Namazi
E-mail: namazisoha@yahoo.com

INTRODUCTION

Treatment of complex diseases often needs the simultaneous use of several drugs. Drug combination therapy can be very effective, whereas multiple

drug therapy is also related to the occurrence of drug–drug interactions (DDIs).^[1] DDIs can cause failure in treatment and adverse drug events (ADEs). Consequent ADEs are highly associated with

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Kheshti R, Aalipour M, Namazi S. A comparison of five common drug–drug interaction software programs regarding accuracy and comprehensiveness. J Res Pharm Pract 2016;5:257-63.

Access this article online



Website: www.jrpp.net

DOI: 10.4103/2279-042X.192461

increased morbidity and mortality.^[2] A review study identified an incidence of up to 2.8% of hospital admissions to be caused by ADEs due to DDIs.^[3]

It is likely that every physician and pharmacist cannot remember and understand all potential DDIs and therefore cannot take corrective actions accordingly. They may be more familiar with drugs used in their specialty but not with drugs used in other specialties. In one study, Glassman *et al.* found that clinicians can correctly recognize only 44% (range 11–64%) of all DDI pairs and 54% of disease-contraindication pairs.^[4] Therefore, an improvement in the clinicians' ability to detect DDIs can reduce the chance of ADEs, preserve patients' safety, and prevent related medical and legal problems.

One of the tools that clinicians trust into review patients' medication sheet for DDIs is computerized DDI software. By manual review of drug regimens by pharmacists, without the use of utility (e.g., drug interaction reference and computer program), only 66% of DDIs in a 2-drug regimen can be correctly identified and the proportion decreases substantially as the number of drugs increases.^[5] While a DDI screening program can be highly desirable, there is concern about variation between programs and about quality and effectiveness of the information. Thus, clinicians should be aware of the advantages and limitations of the DDI applications. In 2001, Hazlet *et al.* reported that up to 33% of relevant drug interactions were not recognized by computer software.^[6] Another problem is the numerous alerts of insignificant drug interactions by software. Clinicians are likely to ignore excessive alerts of unimportant drug interactions, which may also lead to potential unfavorable consequences.^[7]

Among the different computer platforms, the personal digital assistant (PDA) is frequently used for finding drug interactions. Like desktop interaction software, PDA drug interaction software often derives from familiar handbooks, textbooks, and internet sources that can be updated regularly. In addition, PDA software can be accessible at the point of patient care and because of the ease of use are expected to substitute for standard references. Only a few studies have compared some PDA drug interaction software programs such as iFacts, Micromedex, Lexi-Interact, Pharmavista, and Epocrates with each other, to select the best program regarding accuracy, comprehensiveness, and ease of use.^[8,9]

The objective of this study was to evaluate and compare five common PDA drug interaction software programs, which are known by Iranian clinicians in outpatient/inpatient setting, with regard to accuracy and comprehensiveness and to introduce the most reliable software program for clinical practice based on this findings.

METHODS

The last current versions of five drug interaction PDA software programs were obtained from their publishers' website for purposes of this study. Their selection was based on their popularity among Iranian physicians and pharmacists and also reviewing the previous studies.^[8-10] The following software programs were evaluated: Lexi-Interact (v. 1.12.1 (162) ed 2013), Micromedex Drug Interactions (v. 1.46 ed 2013), iFacts (Facts and Comparison's Drug Interactions Facts) (v. 2.9 ed 2013), Medscape (V. 3.2.1 ed 2013), and Epocrates (v. 5 ed 2013). Software was run on a New iPad 3 tablet of Apple™ Company.

To assess the quality of the DDI monographs, 360 unknown interaction pairs (extracted from 360 prescriptions that were randomly selected from two pharmacy affiliated with Shiraz University of Medical Sciences, Shiraz, Iran) and 40 known pairs [Table 1]^[11] were analyzed by each program. One experienced clinical pharmacist was employed as the major reference in identifying DDIs. When the clinical pharmacist could not make a clinical judgment or there was a great difference between her opinion and the software results, we searched the reliable databases (PubMed, Scopus, and Google Scholar) and also the hard copy of Stockley's Drug Interactions^[11] to find information. Each interaction pair was stated by one of the authors, and the clinical pharmacist specified if it was a DDI or not. Moreover, if it was a DDI, the clinical pharmacist specified the severity and level of the interaction. Moreover, then each pair interaction was checked by each program. In this way, the number of true positive (TP), false positive (FP), true negative (TN), and false negative (FN) values was identified for each program. Then, the software programs' sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were determined to assess software accuracy in detecting DDI. Sensitivity was defined as the software's ability to correctly identify clinically important interaction pairs. Specificity was defined as the software's ability to ignore clinically unimportant interaction pairs. The PPV showed the probability that when the software identified a DDI, it was a clinically important interaction. The NPV showed the probability that when the software ignored a DDI, it was a clinically unimportant interaction. Adding the values of sensitivity, specificity, PPV, and NPV and multiplying the sum of them by 100 obtained the accuracy score.^[9]

To assess programs ease of use, the ability of each program to find the management strategy for clinically important DDIs was timed. However, because of the recent advances in computer technology and the high

speed of all DDI screening programs these days (less than a second), we ignored the ease of use in final score

Table 1: Forty known interaction pairs

Number	Interaction pair
1	Furosemide-metoprolol
2	Heparin-ceftriaxone
3	Enoxaparin-omeprazole
4	Imipenem-cefazolin
5	Diazepam-alprazolam
6	Tizanidine-ciprofloxacin
7	Carvedilol-epinephrine
8	Metoprolol-epinephrine
9	Metronidazole-imipenem
10	Amiodarone-warfarin
11	Digoxin-pantoprazole
12	Fentanyl-linezolid
13	Gemfibrozil-clopidogrel
14	Warfarin-sucralfate
15	Tacrolimus-simvastatin
16	Phenytoin-warfarin
17	Spirolactone-digoxin
18	Atorvastatin-warfarin
19	Tramadol-sertraline
20	Ergotamine-propranolol
21	Sumatriptan-lithium
22	Carbamazepine-lithium
23	Captopril-aspirin
24	Aspirin-diclofenac
25	Aspirin-ibuprofen
26	Valproic acid-lamotrigine
27	Clozapine-methimazole
28	Clozapine-propylthiouracil
29	Betahistine-cinnarizine
30	Warfarin-Vitamin K
31	Warfarin-garlic
32	Tamoxifen-warfarin
33	Sertraline-aspirin
34	Calcium carbonate-ranitidine
35	Levothyroxine-sucralfate
36	Verapamil-simvastatin
37	Furosemide-meperidine
38	Levodopa-ferrous sulfate
39	Dopamine-phenytoin
40	Sertraline-clarithromycin

of the programs. To identify the comprehensiveness, each software program was assessed for its ability to detect these elements of a drug interaction monograph: Severity of interaction, onset, mechanism, level of interaction, level of documentation, management, effect (clinical manifestations), case discussion, related drugs, and availability of references. It is of note that these parameters have an important role in detecting and making a clinical judgment about the DDIs. To obtain each program's comprehensiveness score, the number of drug interaction monograph's elements multiplied by 13.4.

The sum of the two factors (accuracy and comprehensiveness) was calculated to obtain the total score for each program. Accuracy and comprehensiveness accounted for 75% and 25% of the total score, respectively. While it is important to get more information about interacting drugs, the most important thing is the accuracy of the information.

The results were analyzed using SPSS version 18 for windows® (IBM Corporation; Armonk, New York, United States. <https://www.ibm.com/marketplace/cloud/statistical-analysis-and-reporting/us/en-us>). Categorical values were reported as percentage. Chi-square test was performed for comparison between categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

The performance of five common DDI screening programs was evaluated. The results of the software programs accuracy and comprehensiveness evaluation are described in Tables 2 and 3, respectively.

The most accurate programs were Lexi-Interact and Epocrates; both of them scored 250 out of 400. The least accurate program was iFacts, scoring 191 out of 400 possible accuracy score. Chi-square test showed that the differences between accuracy scores of programs were statistically significant ($P < 0.001$).

The highest percentage of correct answers (TP plus TN) was received by Lexi-Interact

Table 2: The comparison between 5 software programs for evaluating the 400 pairs of drug-drug interactions s regarding accuracy

Program	TP	FN	TN	FP	Sensitivity	Specificity	PPV	NPV	Accuracy*	P
Epocrates	172	134	69	25	0.56	0.73	0.87	0.33	250	<0.001
iFacts	80	221	65	29	0.26	0.69	0.73	0.22	191	
Lexi-interact	228	68	51	53	0.77	0.49	0.81	0.42	250	
Medscape	147	162	49	42	0.47	0.53	0.77	0.23	202	
Micromedex	125	176	78	21	0.41	0.78	0.85	0.30	236	

*Maximum accuracy score=400. TP=True positive, FN=False negative, TN=True negative, FP=False positive, PPV=Positive predictive value, NPV=Negative predictive value

Table 3: The comparison between 5 drug-drug interaction software programs regarding comprehensiveness

Program	Severity	Onset	Mechanism	Level	Management	Discussion	References	Documentation	Effect	Related drugs	CS*
Epocrates	Yes	No	Yes	Yes	Yes	No	No	No	Yes	No	67
iFacts	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	134
Lexi-interact	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	120
Medscape	Yes	No	Yes	Yes	Yes	No	No	No	Yes	No	67
Micromedex	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	94

*Maximum comprehensiveness score=134

(279 out of 400, 69.8%) and the lowest by iFacts (145 out of 395, 36.7%). The highest percentage of incorrect answers (FN plus FP) was received by iFacts (250 out of 395, 63.3%) and the lowest by Lexi-Interact (121 out of 400, 30.3%). Percentages of correct answers of Epocrates, Micromedex, and Medscape were 60.3% (241 out of 400), 50.8% (203 out of 400), and 49% (196 out of 400), respectively.

Ten possible elements outlined the drug interaction monograph’s comprehensiveness. The most comprehensive DDI screening program was iFacts, providing all 10 possible monographs’ element (Comprehensive Score =134). Lexi-Interact provided 9 out of 10 possible elements and specified as the second program regarding comprehensiveness. The least comprehensive programs were Epocrates and Medscape, each providing only 5 out of 10 possible elements. All programs provided the drug interaction mechanism and management. Only iFacts and Lexi-Interact reviewed the evidence for the interaction, a component that is very important in the patient care setting.

Final score combined the scores of accuracy and comprehensiveness [Table 4]. Lexi-Interact and Micromedex got the highest total score, respectively. About iFacts, although it was the most comprehensive program, it was the least accurate program. Hence, the total score for iFacts was 325 out of 534 and it was ranked third among five programs.

Results showed that 78 DDI pairs (19.5%) had similar severity in all five programs. The results for 150 pairs (37.5%) were similar in three programs and 158 (39.5%) out of them showed similar results in four programs.

DISCUSSION

Clinicians wanted to classify relevant drug interactions, know how to manage them, and differentiate them from irrelevant and unimportant interactions. DDI screening programs are widely used to identify potentially harmful drug interactions in the inpatient and outpatient setting. Halkin *et al.*

Table 4: Comparison between 5 software programs regarding total scores

Program	Accuracy score	Comprehensiveness score	Total score*
Epocrates	250	67	317
iFacts	191	134	325
Lexi-interact	250	120	370
Medscape	202	67	269
Micromedex	236	94	330

*Maximum total score (accuracy + comprehensiveness)=400+134=534

showed that using DDI screening programs by physicians and pharmacists could decrease 67.5% of hazardous DDIs.^[12] What is important is that these programs vary in accuracy and the information within interaction monographs.

An applicable DDI screening program should have both high sensitivity (to detect clinically relevant interactions) and high specificity (to ignore clinically unimportant and irrelevant interactions). If the PPV is too low, many unimportant warnings will confuse the clinician, who may, therefore, miss clinically important interactions.^[13-15] In our analysis, Lexi-Interact showed the highest sensitivity (0.77) and Micromedex showed the highest specificity (0.78). Several studies which have assessed the performance of the DDI screening software programs reported that Lexi-Interact has high sensitivity (87–100%) and specificity (80–90%).^[8,16,17] In total accuracy analysis, Lexi-Interact and Epocrates received the highest score (250 out of 400 each) in our study. In Barron's study that evaluated 9 DDI programs (including iFacts, Mobile Micromedex, Lexi-Interact, Mosby's Drug Consult, Clinical Pharmacology OnHand, Epocrates Rx, Handbook of Adverse Drug Interactions, Mobile PDR, and Tarascon Pharmacopoeia Deluxe), iFacts and Micromedex received the highest accuracy score (both of them scored 390 out of 400).^[8] In that study, Lexi-Interact and Epocrates got third and sixth place, respectively (375 and 344 out of 400, respectively). The difference between his and our study was that Barron's selected three drug interaction references (Facts and Comparisons, Micromedex Drug-Reax, and Hansten and Horn's Drug Interaction and Analysis Management) to identify clinically important and unimportant drug interactions. Clinically important drug interactions were those that identified by all three references as moderate to severe interaction requiring monitoring. Hence, this could have biased the results of the study because Facts and Micromedex were among three gold standards. However, in our study, a clinical pharmacist was considered as gold standard alongside the mentioned Web site and Stockley's Drug Interactions, to identify clinically important interactions. Vonbach *et al.*'s study that evaluated four DDI screening programs (iFacts, Drug-Reax [Micromedex], Lexi-Interact, and Pharmavista) reported the highest precision score for Lexi-Interact.^[9] In their study, the Stockley's Drug Interaction was considered as the gold standard, so they supported our results.

Ten possible elements defined the monograph's comprehensiveness. Receiving 134 out of 134 possible comprehensiveness score, iFacts was the most comprehensive program among the five programs. Our result is similar to Barron's study that reported iFacts and Lexi-Interact as the most

comprehensive resources (both received all possible comprehensiveness score).^[8] However, in our study, Lexi-Interact received 120 out of 134 possible comprehensiveness score. The reason was that in the version of Lexi-Interact that we evaluated, the onset of the interactions was not reported, unlike the previous versions.

On the one hand, we wanted to get more information about the interacting drug (highest comprehensiveness). On the other hand, the resource reliability is very important. Thus, it is important for DDI screening programs to contain a part that shows references related to each interaction monograph. Programs may cite evidence for interaction from a study without a control group to identify confounding factors. An interaction's evidence may also originate from hypothetical or study-based pharmacokinetic findings that do not contain outcomes assessment. Among five programs that we assessed, only two of them (Lexi-Interact and iFacts) included references to interaction evidence. There are, in addition, other deficiencies. Interaction monographs often do not include detectable patient and medication risk factors that make nonsevere drug interactions clinically important. Another problem about the reliability of the programs is a lack of standardization in assigning levels of significance to the interaction.^[18,19] Among the five drug interaction software programs in this study, disagreement on the severity of interactions was seen. Other studies supported our results.^[16,20] This discrepancy in severity rating of identified DDIs between electronic software programs can be explained with inconsistency of evidence and different criteria for the classification of severity of DDIs by various software.^[16]

Many drug interactions are related to the dose of drugs that are consumed together. For example, some drugs may have interaction in high doses, but if they are used in lower doses, they will not lead to interaction. An ideal DDI screening program should be able to ignore an interaction if the drugs are given in doses that will not result in interaction.^[18,21] Among the five programs that we evaluated, none of them had this ability. Other studies reported that the software programs also do not consider dosing of the drugs in the assessment of DDIs.^[17,22] Therefore, one option should be defined in software programs, so clinicians can insert the dose of suspected drugs. Another limitation of 5 understudied drug interaction software programs is that they cannot detect the DDIs regarding duplicate prescription, for example, co-administration of two beta-blockers or two benzodiazepines. In this condition, it is expected that the software will identify the type of interaction as contraindicated. None of the mentioned software

programs was able to detect such an interaction. Hence, improvement is needed to advance the DDI screening programs contribution to detection of DDIs.

Clinical relevance of DDIs evaluated with DDI software is a special concern because software does not consider patient's characteristics, dosing schedule, and precautions taken by the clinicians. Therefore, DDIs detected by the electronic databases may be over-detected compared to the clinician's assessment. Studies reported a high level of discrepancy between the number of DDIs identified by electronic software and the number of clinically relevant DDIs assessed by a clinician.^[23,24] One positive point of the present study is that an expert clinical pharmacist alongside the mentioned web site and Stockley's Drug Interactions was considered as major gold standard. Hence, clinical relevance in the assessment of DDI software was considered.

Finally, our results support previous literature in this area. Studied have indicated variation and deficiencies in DDI screening programs. Of the five drug interaction screening programs evaluated, none was considered to be ideal. However, Lexi-Interact was better than others. Improvement is needed to advance the DDI screening programs contribution to detection of DDIs. A good suggestion is to check interaction pairs by more than one program, for example, two programs and compare their results to achieve more sensitivity. Moreover, as a final point, the clinician's judgment is so important to distinguish relevant from irrelevant interactions.

Lexi-Interact received the highest total score (370 out of 534), followed by Micromedex (330), iFacts (325), Epocrates (317), and Medscape (269), respectively. Hence, Lexi-Interact seems to be the best software program among the programs tested in our study. The point is that all programs have some deficiencies, and they are not thorough alone in detecting DDIs. Thus, simultaneously, an expert specialist is needed to make a final clinical judgment.^[23,24]

AUTHORS' CONTRIBUTION

Soha Namazi designed the study, analyzed the data and edited and approved the article draft. Raziye Kheshti and Mohammadsadegh Aalipour collected and analyzed the data, and wrote the article draft.

Financial support and sponsorship

This study was financially supported by Pharmaceutical Sciences Research Center of Shiraz University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bjerrum L, Andersen M, Petersen G, Kragstrup J. Exposure to potential drug interactions in primary health care. *Scand J Prim Health Care* 2003;21:153-8.
2. 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;111:17-25.
3. Jankel CA, Fitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. *Drug Saf* 1993;9:51-9.
4. Glassman PA, Simon B, Belperio P, Lanto A. Improving recognition of drug interactions: Benefits and barriers to using automated drug alerts. *Med Care* 2002;40:1161-71.
5. Weideman RA, Bernstein IH, McKinney WP. Pharmacist recognition of potential drug interactions. *Am J Health Syst Pharm* 1999;56:1524-9.
6. Hazlet TK, Lee TA, Hansten PD, Horn JR. Performance of community pharmacy drug interaction software. *J Am Pharm Assoc (Wash)* 2001;41:200-4.
7. Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, *et al.* Medication-related clinical decision support in computerized provider order entry systems: A review. *J Am Med Inform Assoc* 2007;14:29-40.
8. Barrons R. Evaluation of personal digital assistant software for drug interactions. *Am J Health Syst Pharm* 2004;61:380-5.
9. Vonbach P, Dubied A, Krähenbühl S, Beer JH. Evaluation of frequently used drug interaction screening programs. *Pharm World Sci* 2008;30:367-74.
10. Abarca J, Colon LR, Wang VS, Malone DC, Murphy JE, Armstrong EP. Evaluation of the performance of drug-drug interaction screening software in community and hospital pharmacies. *J Manag Care Pharm* 2006;12:383-9.
11. Baxter K, Stockley IH. *Stockley's Drug Interactions*. 9th ed. London, UK: Pharmaceutical Press; 2010.
12. Halkin H, Katzir I, Kurman I, Jan J, Malkin BB. Preventing drug interactions by online prescription screening in community pharmacies and medical practices. *Clin Pharmacol Ther* 2001;69:260-5.
13. Magnus D, Rodgers S, Avery AJ. GPs' views on computerized drug interaction alerts: Questionnaire survey. *J Clin Pharm Ther* 2002;27:377-82.
14. Payne TH, Nichol WP, Hoey P, Savarino J. Characteristics and override rates of order checks in a practitioner order entry system. *Proc AMIA Symp* 2002:602-6.
15. Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS. Physicians' decisions to override computerized drug alerts in primary care. *Arch Intern Med* 2003;163:2625-31.
16. Roblek T, Vaupotic T, Mrhar A, Lainscak M. Drug-drug interaction software in clinical practice: A systematic review. *Eur J Clin Pharmacol* 2015;71:131-42.
17. Hadjibabaie M, Badri S, Ataei S, Moslehi AH, Karimzadeh I, Ghavamzadeh A. Potential drug-drug interactions at a referral hematology-oncology ward in Iran: A cross-sectional study. *Cancer Chemother Pharmacol* 2013;71:1619-27.
18. Hansten PD, Horn JR, Hazlet TK. ORCA: Operational classification of drug interactions. *J Am Pharm Assoc (Wash)* 2001;41:161-5.
19. Kelly WN. Potential risks and prevention, part 4: Reports

- of significant adverse drug events. *Am J Health Syst Pharm* 2001;58:1406-12.
20. Van Leeuwen RW, Brundel DH, Neef C, van Gelder T, Mathijssen RH, Burger DM, *et al.* Prevalence of potential drug-drug interactions in cancer patients treated with oral anticancer drugs. *Br J Cancer* 2013;108:1071-8.
 21. Bergk V, Gasse C, Rothenbacher D, Loew M, Brenner H, Haefeli WE. Drug interactions in primary care: Impact of a new algorithm on risk determination. *Clin Pharmacol Ther* 2004;76:85-96.
 22. Reis AM, Cassiani SH. Evaluation of three brands of drug interaction software for use in intensive care units. *Pharm World Sci* 2010;32:822-8.
 23. Bertoli R, Bissig M, Caronzolo D, Odorico M, Pons M, Bernasconi E. Assessment of potential drug-drug interactions at hospital discharge. *Swiss Med Wkly* 2010;140:w13043.
 24. Vonbach P, Dubied A, Beer JH, Krähenbühl S. Recognition and management of potential drug-drug interactions in patients on internal medicine wards. *Eur J Clin Pharmacol* 2007;63:1075-83.