

Personal digital assistant–based drug reference software as tools to improve rational prescribing: Benchmark criteria and performance

Björn C. Knollmann, MD, PhD, Brendan J. Smyth, MD, PhD,
Christine E. Garnett, PharmD, Anastasios N. Salesiotis, MD,
Dragoslav M. Gvozdan, MD, N. Seth Berry, PharmD,
Howard Lee, MD, PhD, and F. David Min, MD *Washington, DC*

CURRENT NEED FOR TOOLS TO IMPROVE RATIONAL PRESCRIBING

The need for rational prescribing, that is, the selection of the most appropriate therapeutic regimen for a specific patient, is greater than ever. For example, a recent study identified physicians' poor prescribing performance as the source for over 70% of clinically significant medication errors in a tertiary-care setting.¹ This may not be surprising given that physicians are expected to incorporate vast amounts of critical information on an ever-increasing number of prescription medications, over-the-counter medications, vitamins, and herbal supplements into prescribing in real time. New data on genetically determined differences in drug action and drug metabolism become available on a daily basis. The problem is further confounded by an aging population with multiple medical problems taking multiple drugs, vitamins, and herbal preparations. Limitations imposed by formulary requirements of health insurance plans and hospital systems further complicate the matter. At the same time, public aware-

ness of prescribing errors as a significant source of preventable patient injuries has risen.² In fact, prescription errors and adverse drug events are a leading cause for malpractice litigation.³

Physicians have always relied on tools such as drug handbooks, pocket cards, and electronic drug databases for rapid access to accurate prescribing information, yet these tools are often limited in scope, are difficult to access, or lack the most current information. The recent advent of electronic drug databases on personal digital assistants (PDAs) holds the promise of giving physicians a new prescribing tool that almost instantaneously provides the most up-to-date and clinically relevant prescribing information and can be directly linked to patient-specific data and laboratory results.⁴ Increasing physician usage of such electronic prescribing tools has been advocated as a means to reduce the number of prescribing errors.^{5,6} Although not yet tested, such an approach seems rational given that lack of pharmacotherapy knowledge has been identified as the primary reason for the poor prescribing performance of physicians resulting in medication errors.¹ This may explain why reliance by physicians on programs such as ePocrates (Epocrates, San Mateo, Calif) has grown exponentially over the last decade, especially among medical students and physicians in training. For example, a survey in 2002 among medical residents found that the majority of respondents used their PDAs daily to access drug reference databases.⁷ At the same time, the number of drug reference software products has risen steeply over the past several years. Although a number of studies have evaluated different PDA-based drug reference software products,⁸⁻¹³ these studies have primarily examined their utility from the perspective of a librarian or a pharmacist.

From the Division of Clinical Pharmacology and Center for Drug Development Sciences, Georgetown University Medical Center.

Supported in part by grants T32GM08386 (B.J.S., C.E.G., A.N.S., and D.M.G.) and R01HL071670 (B.C.K.) from the National Institutes of Health.

Received for publication Jan 25, 2005; accepted March 11, 2005.

Reprint requests: Björn C. Knollmann, MD, PhD, Assistant Professor of Pharmacology and Medicine, Director, Division of Clinical Pharmacology, Georgetown University Medical Center, Med-Dent Building, Room C406, 3900 Reservoir Rd, NW, Washington, DC 20057.

E-mail: knollmb@georgetown.edu

Clin Pharmacol Ther 2005;78:7-18.

0009-9236/\$30.00

Copyright © 2005 by the American Society for Clinical Pharmacology and Therapeutics.

doi:10.1016/j.cpt.2005.03.007

The purpose of this commentary is to suggest a set of benchmark criteria for the utility of PDA-based drug reference software as tools for rational prescribing and to provide an initial assessment on how currently available drug reference software performed when assessed by a novel rating scale based on such benchmark criteria.

BENCHMARK CRITERIA FOR PDA DRUG REFERENCE SOFTWARE AS TOOLS FOR RATIONAL PRESCRIBING

To assemble a list of criteria by which the utility of PDA drug reference software as tools of rational prescribing is assessed, we conducted an informal survey among the fellows and faculty of the Division of Clinical Pharmacology at Georgetown University Medical Center, Washington, DC. All participants had experience in teaching rational prescribing as part of a required therapeutics course for fourth-year medical students.¹⁴ As such, the benchmark criteria primarily reflect the opinion of physicians with training in clinical pharmacology and subspecialty training in internal medicine, oncology, nephrology, pediatrics, and drug development sciences. The following quality criteria were identified.

Up-to-date information

One of the main advantages of electronic databases over printed material is the ability to be updated on a periodic basis. Thus the update frequency of an electronic database represents a significant quality criterion for its clinical utility as a prescribing tool.

Evidence-based dosing information for labeled and unlabeled indications

In addition to the standard information on indications, dosage, frequency, route of administration, dosage forms, contraindications, and precautions, rational prescribing tools should contain the following in the drug monograph: (1) dosage recommendations for special populations (eg, pediatric patients, geriatric patients, pregnant women, and patients with renal impairment), (2) estimates of the level of evidence that supports the use of a drug for a particular indication (eg, randomized, placebo-controlled trial), and (3) estimates of the anticipated size of drug effect (eg, number needed to treat). Such data should be provided for both labeled and unlabeled indications. This information would allow the prescriber to better estimate the risk-benefit ratio of a given drug for an individual patient. It would also help the prescriber to choose between alternative treatment options.

Structured information on side effects of drugs

To maximize the utility to the prescriber, possible side effects should not merely be listed, but information should be structured to give the frequency and severity of each side effect. In addition, recommendations on how to manage side effects and drug toxicity (ie, overdose) should be provided.

Structured information on drug interactions

Any good electronic prescribing tool should contain comprehensive information on drug-drug, drug-food, and drug-herbal interactions. The information should be structured to provide the likelihood and severity of the interactions, explain the underlying mechanism in brief, and give recommendations for clinical management of the interaction. In addition, the electronic prescribing tool should be capable of screening a list of drugs, herbals, and food items for possible drug interactions.

Herbals and nutritional supplements

Given the high prevalence of use of herbals and nutritional supplements among patients, any good drug database should contain basic information (eg, claimed benefits, dosage, contraindications, and side effects) on herbals and nutritional supplements.

Special features

Good drug reference software should contain a number of special features that would further help the prescriber to select the most appropriate drug and dosage for a specific patient. In particular, features such as medical calculators, treatment guidelines based on national consensus documents, pharmacokinetic information, free-text search capability, drug cost information, drug picture, compatibility of intravenous solutions, and cross-referencing of drug information to the Internet and the medical literature would significantly enhance the utility of a prescribing tool.

The above features should ideally be combined in a single user interface that provides quickly accessible, searchable, and cross-referenced prescribing information. At the same time, the information should be comprehensive in scope.

DEVELOPMENT OF A RATING SCALE FOR PDA-BASED DRUG REFERENCE SOFTWARE AS RATIONAL PRESCRIBING TOOLS

The benchmark criteria identified above were used to develop a 40-point rating scale to compare different software products (Table I). Each criterion was weighted depending on how important we thought it

was for a rational prescribing tool. For example, information on indication and dosage was considered most important and was weighted with 10 points. Information on side effects, drug interactions, and special features was weighted with 8 points each. The availability of an herbal and nutritional supplement database was considered the least important feature and was weighted with only 2 points.

For the main quality criteria of prescribing software products identified in the previous section (eg, the presence of rational prescribing features such as evidence-based dosage recommendations, structured information on drug interactions and side effects, and searchable drug database), 4 to 8 points were given, depending on whether the prescribing features were present (see Table I for details). As a result, rational prescribing features represented a total of 22 points, or 55% of the maximally possible score.

To also obtain a comprehensiveness score for indication, side effect, and drug interaction data, rather than comparing the results against a gold standard, software products were assigned points based on their quintile rank: products ranking in the top quintile received 4 points, and products ranking in the bottom quintile received no points. Together with the herbal category, a total of 14 points (35% of total score) were possible for comprehensiveness. Update frequency was tested by assessing whether drugs with different approval dates were contained in the database and was rated on a scale from 0 to 4.

A battery of drugs, foods, and nutritional supplements was then used to assess the performance of the different software products (see Table I). The drug indication and side effect data were evaluated with 3 test drugs that have numerous labeled and unlabeled indications, have an extensive side effect profile, and represent 3 different drug categories: generic (carbamazepine), over the counter (acetaminophen), and brand name (sildenafil). To evaluate whether the drug reference software can provide the most rational evidence-based dosage recommendation, gentamicin was used as a test drug. Once-a-day or extended interval dosing of aminoglycosides such as gentamicin has clearly been established as at least as efficacious and possibly less side effect-prone for adults^{15,16} and children¹⁷ compared with traditional multiple daily dosing regimens. Once-a-day aminoglycoside dosing could be considered the standard of care for adult patients, given that such regimens have been adopted by more than 75% of US hospitals surveyed in 2000.¹⁸

The drug interaction data were evaluated by use of 3 sets of drug-herbal, drug-drug, and drug-food combinations. The first set—cyclosporine (INN, ciclosporin) and St John's wort—was chosen to represent a well-documented, potentially life-threatening drug-herbal interaction.^{19,20} The second set—carbamazepine, sildenafil, acetaminophen, ethanol, and grapefruit juice—was chosen to test whether the software can detect drug-food interactions in a list of multiple drugs and food. The final set—erythromycin and ketoconazole—was chosen to test whether the software could predict a potentially life-threatening drug interaction (cardiac arrhythmia) based on established pharmacologic principles. This drug interaction is plausible because it is well established that ketoconazole inhibits cytochrome P450 (CYP) 3A4,²¹ the P450 enzyme that metabolizes erythromycin.²² Although neither pharmacokinetic interaction data nor increased incidences of QT prolongation or cardiac arrhythmia have been reported for the ketoconazole-erythromycin combination, increased erythromycin blood concentrations resulting from ketoconazole coadministration are clearly a risk factor for QT prolongation, torsades de pointes cardiac arrhythmias, and sudden death.²³

SURVEY OF AVAILABLE PDA-BASED ELECTRONIC DRUG REFERENCE SOFTWARE

An Internet search conducted in August 2003 identified 11 PDA-based electronic databases that fulfilled at least 5 of the above quality criteria: 5 stand-alone products and 6 software suites. Software suites were defined as individual databases that can be combined into the same user interface and are cross-linked. Products that covered only specific areas (eg, drug interactions, herbal databases) or were merely electronic reproductions of handbooks published annually were not included in the analysis. All products surveyed could be frequently updated via download from the company's Web site. In all cases the updates were performed automatically during the hot-sync process of the handheld device. Prices ranged from \$27 to \$155 for an annual license. For a number of products (Pepid, CP OnHand, ePocrates, and mobileMDX), the use was restricted to the 1-year term. For the remainder, the products were still usable after 1 year, but no further updates were provided. All products were available for either the Palm or PocketPC operating system. The size of the drug database varied considerably among products, ranging from 900 to over 7000 drug names. Table II summarizes the basic features of the 11 products; it was updated

Table I. Rating scale to evaluate PDA-based drug reference software

PDA rating scale (range of possible scores)	Stand-alone software products					
	CP OnHand	ePharmacopoeia	ePocrates	mobileMDX	mobilePDR	Pepid PDC
Update frequency						
Which of the following drugs are in the database (yes = 1, no = 0)?						
Aciphex (rabeprazole), NDA 9/30/02	1	1	1	1	1	1
Gleevec (imatinib), NDA 4/18/03	1	1	1	1	1	1
Aggrastat (tirofiban), NDA 2/28/03	1	1	1	1	1	1
Levitra (vardenafil), NDA 8/19/03	1	0	0	0	0	0
Update frequency score (0-4)	4	3	3	3	3	3
Indications and dosing						
Which of the following features are present (yes = 1, no = 0)?						
1. Labeled and unlabeled indications	1	1	1	1	0	1
2. Dosing in special populations	1	1	1	1	1	1
3. Level of evidence for efficacy	0	0	0	0	0	0
4. Drug effect size	0	0	0	0	0	0
5. Gentamicin ODD listed	1	1	1	0	1	1
6. Gentamicin ODD as primary regimen	0	0	0	0	0	0
Indications and dosing features (0-6)	3	3	3	2	2	3
How many indications are present for each of the following drugs?						
1. Carbamazepine	12	4	4	7	3	7
2. Acetaminophen	9	3	2	2	8	3
3. Sildenafil	4	1	1	1	1	1
Raw score	25	8	7	10	12	11
Indications comprehensiveness (0-4)	4	1	1	1	2	2
Combined score for indications (0-10)	7	4	4	3	4	5
Side effects and toxicity						
Which of the following side effect features are present (yes = 1, no = 0)?						
1. Side effects listed	1	1	1	1	1	1
2. Frequency listed	0	1	0	1	0	1
3. Severity rated	0	1	1	1	1	0
4. Management recommendations	0	0	0	1	0	1
Side effect features (0-4)	1	3	2	4	2	3
How many side effects are listed for the following drugs?						
1. Carbamazepine	74	16	34	43	15	14
2. Acetaminophen	23	3	11	6	0	5
3. Sildenafil	44	11	23	10	8	8
Total raw score	141	30	68	59	23	27
Side effect comprehensiveness (0-4)	4	1	2	2	0	0
Combined score for side effects (0-8)	5	4	4	6	2	3

Data reflect software product versions that were updated from the respective company Web sites on August 19, 2003, and evaluated during the month of September 2003. Software products evaluated: CP OnHand (Gold Standard Multimedia, Tampa, Fla), ePharmacopoeia (Tarascon Publishing, Lompoc, Calif), ePocrates (Epocrates), mobileMDX (Thomson Healthcare, Montvale, NJ), mobilePDR (Thomson Healthcare), Pepid Portable Drug Compendium (PDC; Pepid LLC, Skokie, Ill), A2zDrugs (Skyscape, Marlborough, Mass), Clin-eRX (Skyscape), DrDrugs (Skyscape), Lexi-Drugs (Lexi-Comp, Hudson, Ohio), and PDRDrugs (Skyscape).

NDA, New Drug Application; PDA, personal digital assistant; ODD, once-daily dosing.

*Combined with iFacts drug interaction database.

†Combined with Lexi-Interact and Lexi-Natural Products databases.

Software suites

<i>A2zDrugs*</i>	<i>Clin-eRX*</i>	<i>DrDrugs*</i>	<i>Lexi-Drugs†</i>	<i>PDRDrugs*</i>
1	1	1	1	1
1	1	1	1	1
1	1	1	1	1
0	0	0	0	0
3	3	3	3	3
1	1	1	1	1
1	1	1	1	1
0	0	0	0	0
0	0	0	0	0
0	1	1	1	1
0	0	0	0	0
2	3	3	3	3
3	3	6	11	3
2	3	2	2	2
1	1	1	3	1
6	7	9	16	6
1	1	1	3	1
3	4	4	6	4
1	1	1	1	1
1	0	1	1	1
0	0	1	1	1
0	0	0	1	0
2	1	3	4	3
15	8	27	76	16
9	1	5	10	9
122	5	15	39	120
146	14	47	125	145
4	0	1	4	4
6	1	4	8	7

Table I—Cont'd

PDA rating scale (range of possible scores)	Stand-alone software products					Pepid PDC
	CP OnHand	ePharmacopoeia	ePocrates	mobileMDX	mobilePDR	
Drug interactions						
Which of the following drug interaction features are present (yes = 1, no = 0)?						
1. Drug interactions listed	1	1	1	1	1	1
2. Severity rated	1	1	0	1	0	1
3. Mechanism described	1	1	1	1	1	1
4. Dosing adjustments recommended	1	1	1	1	0	1
Drug interaction features (0-4)	4	4	3	4	2	4
How many drug-drug, drug-food, and drug-herbal interactions are listed?						
1. St John's wort and cyclosporine	1	0	1	0	0	0
2. Carbamazepine, acetaminophen, sildenafil, ethanol, and grapefruit juice	6	3	4	1	1	3
3. Ketoconazole and erythromycin	0	1	0	0	0	3
Total raw score	7	4	5	1	1	6
Interaction comprehensiveness (0-4)	3	2	2	0	0	3
Combined score for drug interactions	7	6	5	4	2	7
Herbals						
How many names of herbals, supplements, or alternative medicines are present?						
Scoring (0 = 0, 1-150 = 1, and >150 = 2)	25	50	477	256	0	200
Total score for herbals and supplements (0-2)	1	1	2	2	0	2
Special features						
Which of the following special features are present (yes = 1, no = 0)?						
1. Medical calculators	0	1	1	0	0	1
2. Tables and therapeutic algorithms	0	1	1	0	1	1
3. Search capability	0	0	0	0	0	0
4. Pharmacokinetic data	0	0	1	0	0	1
5. Drug cost	0	1	1	0	0	1
6. Intravenous compatibility	0	0	0	0	0	1
7. Drug picture available	0	0	0	0	0	0
8. Data hyperlinked to Internet resources	0	0	0	0	0	0
Total special features score (0-8)	0	3	4	0	1	5
Total						
Total score (0-40)	24	21	22	18	12	25
Percentage score (0%-100%)	60%	53%	55%	45%	30%	63%
Rank among drug reference software	3	5	4	9	11	2

to reflect product versions available for purchase in December 2004.

PERFORMANCE OF PDA-BASED DRUG REFERENCE SOFTWARE AS RATIONAL PRESCRIBING TOOLS

There was a large range in the performance of the different drug reference software products when as-

sessed by the 0- to 40-point rating scale. The lowest-scoring product, mobilePDR, had only 30% (12 points) of the quality criteria and scope considered important for a rational prescribing tool, whereas the highest-scoring product, Lexi-Drugs, achieved 73% (29 points). Table I describes the point scores of the different software products in detail for each prescribing category.

<i>Software suites</i>				
<i>A2zDrugs*</i>	<i>Clin-eRX*</i>	<i>DrDrugs*</i>	<i>Lexi-Drugs†</i>	<i>PDRDrugs*</i>
1	1	1	1	1
1	1	1	1	1
1	1	1	1	1
1	1	1	1	1
4	4	4	4	4
1	1	1	1	1
4	4	4	6	4
0	0	0	1	0
5	5	5	8	5
2	2	2	4	2
6	6	6	8	6
0	0	30	175	0
0	0	1	2	0
0	0	0	0	0
0	1	0	0	1
0	0	0	0	0
1	1	1	1	0
0	0	0	1	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
1	2	1	2	1
19	16	19	29	21
48%	40%	48%	73%	53%
7	10	7	1	5

Up-to-dateness

All products contained data on drugs approved by the Food and Drug Administration within the last year period, suggesting that the delivery of up-to-date information is achieved, which is surely 1 of the strongest aspects of PDA-based drug reference software. CP On-Hand was the only product that provided information on drugs that were in the late phase of clinical devel-

opment and had not yet been approved and thus scored highest in this category.

Information structure and rational prescribing features

As outlined above, providing structured information on indications, side effects, and drug interactions, as well as special prescribing features, was considered the

Table II. Overview of PDA-based drug reference software

<i>Name (URL)</i>	<i>Price (\$)*</i>	<i>Company</i>	<i>Size (MB)†</i>	<i>No. of drug names</i>	<i>Comments</i>
Stand-alone drug reference software					
CP OnHand (www.cponhand.gsm.com)	99	Gold Standard Multimedia	16.4	6700	IV Alert costs additional \$49 annually
ePharmacopoeia (www.tarascon.com)	27	Tarascon Publishing	4.0	>4000	Drug interaction tool based on Medical Letter database
ePocrates Rx Pro (www.epocrates.com)	60	Epocrates	3.8	3400	Regular ePocrates Rx available free to physicians and medical students
mobileMDX (www.micromedex.com)	75	Thomson Healthcare	8.3	3200	Available free with institutional subscription
mobilePDR (www.mobilepdr.com)	60	Thomson Healthcare	3.9	No information	Available free to physicians and medical students
Pepid PDC (www.pepid.com)	70	Pepid LLC	5.7	5000	Pepid Portable Drug Compendium (PDC) is included at no charge with any clinical suite
Software suites§					
A2zDrugs and iFacts (www.skyscape.com)	108‡ (50 + 70)	Facts and Comparisons	4.3 and 3.3	>5000	
PDRDrugs and iFacts (www.skyscape.com)	120	Thomson Healthcare	2.1 and 3.3	>1500	Not currently available
Clin eRx and iFacts (www.skyscape.com)	90 (20 + 70)	McGraw-Hill	0.8 and 3.3	>1000	
DrDrugs and iFacts (www.skyscape.com)	108‡ (50 + 70)	F.A. Davis	2.4 and 3.3	>4000	
Lexi-Drugs, Lexi-Interact, and Lexi-Natural Products (www.lexi.com)	155‡ (75 + 75 + 75)	Lexi-Comp	5.3, 2.8, and 0.3	7000	Each additional database is \$40

With the exception of PDR Drugs, data reflect product versions updated from the respective company Web sites on December 21, 2004.

*Price either for annual usage license or for product purchase with free updates for a 1-year period.

†Size of software when installed on Tungsten C with Palm OS.

‡Discounted price when purchased together as software suite.

§Suites provide a single user interface that links separate drug or natural product databases (or both) with drug interaction software (iFacts from Skyscape and Lexi-Interact from Lexi-Comp).

most important aspect for a rational prescribing tool. Accordingly, points in this category reflected more than 50% of the overall score (22/40). As illustrated in Fig 1, even the highest-scoring product, Pepid PDC, had only 70% of the features considered essential for a good prescribing tool. Many products had less than 50%, with mobilePDR and CP OnHand scoring lowest in this category. The overall average of $50\% \pm 11\%$ suggests that there is significant room for improvement for the different software products. There was also significant

variability in how different products performed in each category. This is discussed below.

Indications and dosage. With the exception of mobilePDR, all products contain information on drug use for labeled and unlabeled indications and on dosing in special populations. However, because none of the software products provided information on the level of evidence that supports the use of a drug for a particular indication or on the anticipated size of drug effect, one would have to rate the performance of all products as

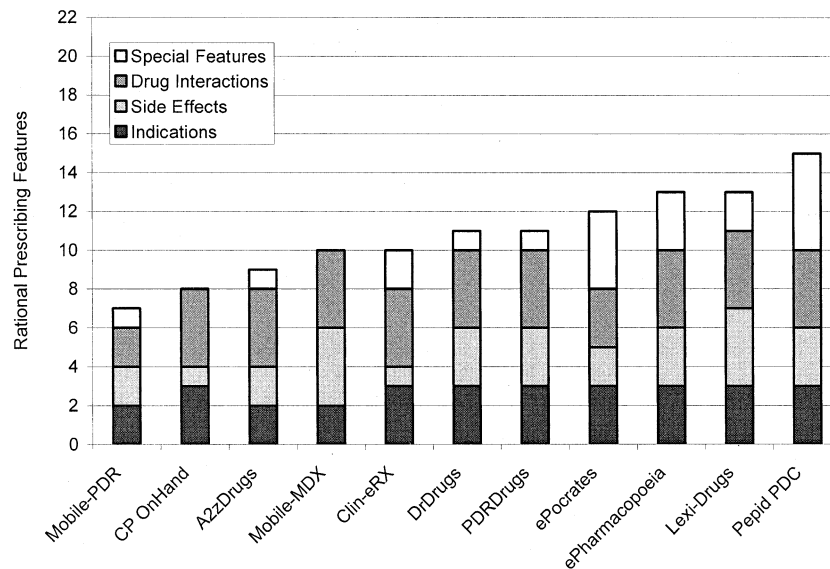


Fig 1. Comparison of rational prescribing features. The following categories from Table I are included in the score for rational prescribing features: structured information on indications and dosing (0-6 points), side effects (0-4 points), drug interactions (0-4 points), and special features (0-8 points).

mediocre in this category. The only exception was CP OnHand, which summarized data from published studies that support the use of a particular drug for unlabeled indications but did not provide any specific references.

Evidence-based dosage recommendations. None of the software products recommended once-a-day gentamicin dosing as the primary dosing regimen. Of the 11 programs, 9 mentioned it as an alternative dosing regimen. A2zDrugs and mobilePDR did not list it at all.

Side effects and toxicity. Products differed widely in the category of side effects and toxicity. Although all software products listed side effects, only 2 (Lexi-Drugs and mobileMDX) provided structured information on the frequency, severity, and clinical management of side effects and drug overdoses. Interestingly, both the largest database (CP OnHand) and the smallest database (Clin-eRX) scored lowest in this category.

Drug interactions. The drug interaction category was a significant strength of drug reference software because all programs except ePocrates and mobilePDR had all of the drug interaction features that we would expect from a good prescribing tool. However, this was also the only category where all of the databases contained significant errors (see below for details).

Special features. The special features category represents a significant weakness of the currently available

drug reference software products. None of the products had a free-text search capability or drug pictures. None was able to hyperlink drug data to Internet resources (eg, PubMed). Only 1 product, Pepid PDC, provided information on the compatibility of various intravenous solutions (eg, total parenteral nutrition, 5% dextrose injection, 0.9% sodium chloride injection, and 8.5% amino acid injection). CP OnHand and mobileMDX had no special prescribing features whatsoever. Even the overall highest-scoring product, Lexi-Drugs, did not have medical calculators or treatment algorithms. Pepid PDC and ePocrates scored highest in this category.

Comprehensiveness of information

The comprehensiveness of drug information was assessed for indications, side effects, drug interactions, and herbals. Fig 2 compares the scores of the different products. The size of the database clearly played a role in determining the score in this category. For example, the largest databases (CP OnHand, 16 MB) scored high, and the smallest product (Clin-eRX, 0.8 MB) scored low. However, factors other than database size were also important, because the highest-scoring product, Lexi-Drugs, and the lowest-scoring product, mobilePDR, were of similar size (5.3 MB and 3.9 MB, respectively).

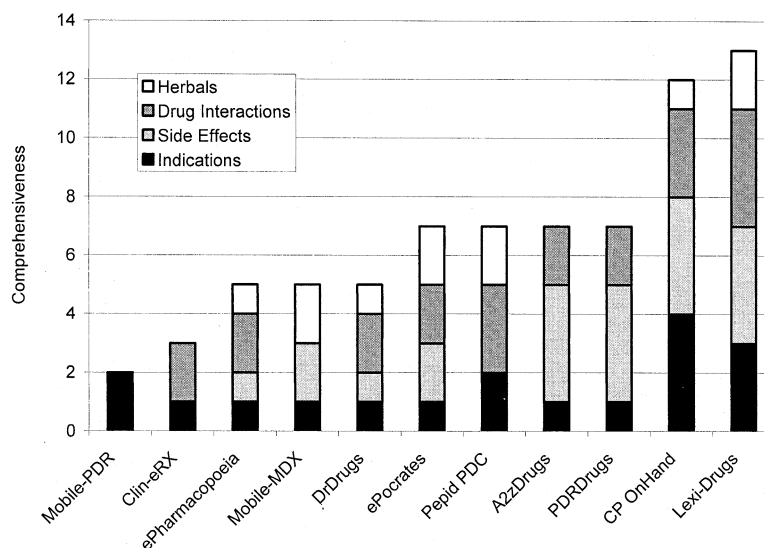


Fig 2. Comparison of database comprehensiveness. The following categories from Table I are included in the score for comprehensiveness: labeled and unlabeled indications (0-4 points), side effects (0-4 points), drug interactions (0-4 points), and herbal database (0-2 points).

Accuracy of information

A surprising finding was that even in our limited evaluation using several test drugs, every drug reference software product contained errors in its ability to detect clinically significant drug interactions. Three products (mobilePDR, mobileMDX, and ePharmacopoeia) were not able to detect potentially life-threatening herbal-drug interactions because their respective drug interaction tools could not screen for herbal medications. One product (Pepid PDC) did detect the St John's wort–cyclosporine interaction but misclassified the interaction as minor, not clinically significant. None of the products could correctly identify the potential risk of a ketoconazole-erythromycin combination for QT prolongation and cardiac arrhythmias. The 3 products that detected the interaction classified it as minor, of questionable clinical significance.

No significant errors were detected in the drug monograph information on labeled indications, dosage, and side effects. Accuracy of herbal information was not assessed. CP OnHand contained a number of programming errors, such as duplication of monograph pages or incorrect linkage of drug and side effects (eg, wrong side effects listed for acetaminophen [INN, paracetamol]). The latter was corrected in a version obtained in December 2004.

Re-evaluation of drug interaction data

Given the significant errors identified in all of the drug interaction databases, we decided to re-evaluate

the drug interaction component of the different products in December 2004, approximately 15 months after the initial purchase. The results were somewhat disappointing: only 4 (CP OnHand, ePharmacopoeia, ePocrates, and Pepid PDC) of 11 products were able to correctly identify potentially serious consequences of the ketoconazole-erythromycin interaction. This was the case even after a study published in October 2004 in the *New England Journal of Medicine* strongly advised against the concomitant use of erythromycin with strong CYP3A4 inhibitors such as ketoconazole.²⁴ Furthermore, mobilePDR, mobileMDX, and ePharmacopoeia were still unable to screen for drug-herbal interactions. The new version of Pepid PDC correctly identified the cyclosporine–St John's wort interaction.

COMPARISON WITH PREVIOUSLY PUBLISHED EVALUATIONS OF PDA-BASED DRUG REFERENCE SOFTWARE

On the basis of the data presented here (Table I), Lexi-Drugs and Pepid PDC presently provide the best combination of features (Fig 1) and comprehensiveness (Fig 2) as rational prescribing tools for physicians. In contrast, mobilePDR had significant deficiencies across all categories and cannot be recommended as a first-line mobile prescribing reference. Programs such as CP OnHand and mobileMDX have a wealth of drug information and may have significant potential in the future if made more user friendly for physicians. From our

analysis, it also appears that currently available PDA-based drug reference products come in 2 flavors: programs that evolved out of pharmacy reference databases (eg, mobileMDX and CP OnHand) and programs that evolved out of drug references for medical students and physicians (eg, ePharmacopoeia, ePocrates, and Pepid PDC). As a result, programs such as CP OnHand excel in the comprehensiveness and quality of drug information (Fig 2) but fall short in providing prescribing features important to physicians (Fig 1). The opposite appears to be the case for programs such as ePharmacopoeia. Interestingly, ePocrates, which is currently the PDA drug reference that is most widely used among physicians,²⁵ was average in both categories (Figs 1 and 2).

Using a validated set of drug questions critical to pharmacists, Clauson et al⁸ recently compared scope, completeness, and ease of use of PDA-based drug reference software. With the exception of Pepid PDC, the same drug reference products were included in their study. Overall, their results were consistent with our study in that Lexi-Drugs ranked highest and mobilePDR ranked lowest. Although they did not assess it formally, these authors also concluded that the only significant errors were found in the drug interaction database. These results confirm an earlier survey that also ranked Lexi-Drugs highest.⁹ It should be noted that none of these studies considered the clinical utility of drug reference software for physicians, which may explain why Pepid PDC was not included in any of the previous studies. Pepid PDC, which ranked highest in terms of rational prescribing features in our analysis, was developed as part of a suite of medical decision-making products for physicians.

Barrons²⁵ recently compared the accuracy, comprehensiveness, and ease of use of PDA-based drug interaction software. Again, with the exception of Pepid PDC, all of the products covered in our study were included in his review. Similar to our results, iFacts and Lexi-Interact scored highest overall and mobileMDR scored lowest. CP OnHand had the highest score for sensitivity of detected drug-drug interactions but scored lowest in usability. Drug-food or drug-herbal interactions were not assessed in this study. The author noted that both iFacts and Lexi-Drugs were more accurate than several drug interaction databases used routinely by pharmacies. The lack of a rating of the severity of the drug interaction was cited as one of the deficiencies in several database products.²⁵ This appears to have been corrected in the more current versions of the drug interaction products examined here (Table I).

Medical students and physicians in training (interns, residents, and fellows), who usually do not have routine access to office-based drug reference software, currently are the primary consumer of PDA-based drug reference software.⁷ Thus such software products should strive to educate their users by providing evidence-based drug information. For example, information on the mechanism of action, size of drug effect, level of evidence, and literature references for specific indications, side effects, or drug interactions would be valuable. Unfortunately, among the currently available software products, such an approach has been taken only for drug interactions and only by a few products (Lexi-Interact, iFacts, and ePharmacopoeia). This is unfortunate, because the availability of inexpensive memory expansion cards makes the size of the drug database much less of a concern. Furthermore, intelligent and user-friendly structuring and linking of drug information also remain an issue. For example, it is surprising that none of the databases provided a free-text search tool that would allow the user to retrieve information in the database specific to his or her questions.

It should be recognized that the evaluation of up-to-dateness, comprehensiveness, and accuracy was only a snapshot using a small number of test drugs and drug combinations and, therefore, may not reflect the overall database. Furthermore, product accuracy and ease of use were not reflected in the overall score. However, our results were largely consistent with the results of studies that examined individual components of the databases in greater detail.^{8,25} We would encourage the reader to also consult these studies before selecting an individual product. Given that software companies continually update their content and features, reviews such as ours should be conducted regularly. At the same time, it is hoped that the companies will respond to the criticisms raised here and address them in the next versions of the software products. It should be remembered that, though likely, it remains to be determined whether use of better PDA-based drug reference products will improve rational prescribing and reduce medication errors.

To summarize, the spectrum of currently available PDA-based drug reference software products provides physicians with a range of reasonable prescribing tools from which to choose. Their major strengths are the provision of up-to-date information on indications, dosage, and detection, rating and management of drug interactions, and side effects. Their major weaknesses as rational prescribing tools are as follows: (1) lack of information on the scientific evidence and size of drug

effect for specific indications, (2) lack of free-text search capability, (3) lack of data linkage to Internet resources, and (4) inaccuracy of drug interaction information. Hopefully, these weaknesses will be addressed in future versions of the drug reference products. Meanwhile, given the large range of performance of the different products across different prescribing categories, it may be advisable for physicians to use not just 1 but 2 or 3 different products as prescribing tools.

We thank Yvonne M. Hernandez for her helpful suggestions and proofreading of the manuscript.

All of the authors have no conflict of interest related to the content of this manuscript. None of the software companies mentioned in this article provided any financial support for this study.

References

1. Winterstein AG, Johns TE, Rosenberg EI, Hatton RC, Gonzalez-Rothi R, Kanjanarat P. Nature and causes of clinically significant medication errors in a tertiary care hospital. *Am J Health Syst Pharm* 2004;61:1908-16.
2. Kohn L, Corrigan J, Donaldson M, editors. *To err is human: building a safer health system*. Washington, DC: Committee on Quality of Health Care in America, Institute of Medicine, National Academy Press; 2000.
3. De Sousa B. Prescription problems: clinical pharmacology and lawsuits. *Tex Med* 1996;92:58-60.
4. Cimino JJ, Bakken S. Personal digital educators. *N Engl J Med* 2005;352:860-2.
5. Robinson RL, Burk MS. Identification of drug-drug interactions with personal digital assistant-based software. *Am J Med* 2004;116:357-8.
6. Rosenbloom M. Medical error reduction and PDAs. *Int Pediatr* 2003;18:69-77.
7. Barrett JR, Strayer SM, Schubart JR. Assessing medical residents' usage and perceived needs for personal digital assistants. *Int J Med Inform* 2004;73:25-34.
8. Clauson KA, Seamon MJ, Clauson AS, Van TB. Evaluation of drug information databases for personal digital assistants. *Am J Health Syst Pharm* 2004;61:1015-24.
9. Enders SJ, Enders JM, Holstad SG. Drug-information software for Palm operating system personal digital assistants: breadth, clinical dependability, and ease of use. *Pharmacotherapy* 2002;22:1036-40.
10. Keplar KE, Urbanski CJ. Personal digital assistant applications for the healthcare provider. *Ann Pharmacother* 2003;37:287-96.
11. Lowry CM, Kostka-Rokosz MD, McCloskey WW. Evaluation of personal digital assistant drug information databases for the managed care pharmacist. *J Manag Care Pharm* 2003;9:441-8.
12. McCreadie SR, Stevenson JG, Sweet BV, Kramer M. Using personal digital assistants to access drug information. *Am J Health Syst Pharm* 2002;59:1340-3.
13. Corley PM. Drug handbooks for personal digital assistants (PDAs): a comparison of ePocrates Rx, Lexi-Drugs Platinum, mobile MICROMEDEX, and Tarascon e-Pharmacopoeia. *J Med Libr Assoc* 2002;90:489-93.
14. Flockhart DA, Usdin Yasuda S, Pezzullo JC, Knollmann BC. Teaching rational prescribing: a new clinical pharmacology curriculum for medical schools. *Naunyn Schmiedeberg's Arch Pharmacol* 2002;366:33-43.
15. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997;24:796-809.
16. Barza M, Ioannidis JP, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: a meta-analysis. *BMJ* 1996;312:338-45.
17. Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JP. Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004;114:e111-8.
18. Chuck SK, Raber SR, Rodvold KA, Areff D. National survey of extended-interval aminoglycoside dosing. *Clin Infect Dis* 2000;30:433-9.
19. Breidenbach T, Kliem V, Burg M, Radermacher J, Hoffmann MW, Klempnauer J. Profound drop of cyclosporin A whole blood trough levels caused by St. John's wort (*Hypericum perforatum*). *Transplantation* 2000;69:2229-30.
20. Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G. Acute heart transplant rejection due to Saint John's wort. *Lancet* 2000;355:548-9.
21. Varhe A, Olkkola KT, Neuvonen PJ. Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994;56:601-7.
22. Paine MF, Wagner DA, Hoffmaster KA, Watkins PB. Cytochrome P450 3A4 and P-glycoprotein mediate the interaction between an oral erythromycin breath test and rifampin. *Clin Pharmacol Ther* 2002;72:524-35.
23. Drici MD, Knollmann BC, Wang WX, Woosley RL. Cardiac actions of erythromycin: influence of female sex. *JAMA* 1998;280:1774-6.
24. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004;351:1089-96.
25. Barrons R. Evaluation of personal digital assistant software for drug interactions. *Am J Health Syst Pharm* 2004;61:380-5.