Computer-Assisted Evaluation of Adverse Events Using a Bayesian Approach

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The differential diagnosis of idiosyncratic adverse drug reactions (ADRs) is complex because for each adverse event there are many possible drug and nondrug causes. Recently efforts have been made to computerize causality assessment methods. A new computerized, user-friendly diagnostic aid for Bayesian assessment of adverse drug events (MacBARDI-Q&A) is described. This computer program performs a differential diagnosis on cutaneous reactions suspected of being drug-induced. The authors' results indicate that development of a valid, simple and user-friendly computerized procedure for evaluating adverse drug events is possible. The ongoing development and application of MacBARDI-Q&A and other similar programs should improve the evaluation of putative adverse drug reactions.

Over the past two decades, various computerized decision aids have been developed to ease the burden on physicians caused by the steady expansion of medical knowledge and to facilitate the use of complex models for medical diagnosis. Computer programs have been developed to act as a consultant in a timely fashion for various problems such as acute abdominal pain,[1] electrolyte disorders,[2] and challenging problems in internal medicine.[3]

There are three different inferential bases that have been applied to medical decision-making: (1) algorithms; (2) statistical methods (includes Bayes' theorem); and (3) artificial intelligence. An algorithm has been defined as a problem-specific flowchart containing step-by-step instructions on how to arrive at an answer.[4] Of the second group, the most common statistical method for differential diagnosis has been the Bayesian model,[5,6] which takes an initial probability estimate and uses additional patient-specific information to modify this probability and calculate the likeliest diagnosis. The third basis, artificial intelligence, is a computer science subfield that uses non-numeric symbol processing to mimic human thinking.[5] Each of these has advantages and limitations.[7]

Early computerized medical decision aids frequently used algorithms as an inferential basis.[5] These algorithms had originally been designed by clinicians and then were computerized. The use of algorithms as models for medical diagnosis is limited, however, because they lack flexibility.[5,6] For example, there may be information that the clinician thinks is important to include, yet there is no relevant question in the algorithm. If the corresponding question is added, the whole algorithm must be reweighted and tested, making them difficult to modify.[5] Also, if case-specific questions are added as needed, algorithms quickly become too large to manage.[7] Furthermore, because each question typically requires a "yes" or "no" answer, it is difficult to apply when the information is missing or uncertain.[7] Because these computerized methods are conveniently and easily applied by hand, there is no obvious advantage gained by computerization.[6] Because of these problems, statistical methods and artificial intelligence are now more common inferential bases for computerized diagnostic aids.[4,5]

Recently, computer-assisted diagnosis has been applied to the differential diagnosis of suspected adverse drug reactions, called adverse drug events (ADEs). The differential diagnosis of ADEs is chal-

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lenging for a physician because each event can have multiple possible drug and nondrug causes and diagnostic tests that can distinguish between these causes are rare. In fact, experts frequently disagree when asked to determine the strength of a causal relationship between a given drug and an adverse event.[8,9]

Early solutions to this problem were frequently in the form of standardized decision aids (SDAs) or algorithms.[10] Standardized decision aids are a group of causality assessment methods that have several features in common: they pose a series of predetermined questions; the question are usually answered "yes", "no" or, sometimes "unknown/not applicable"; the answers to each of the questions has a preset weight, and they are combined in an explicit manner; and the final weight score then is converted to a probabilistic statement regarding the strength of the causal relationship such as "possibly" or "probably" drug related. These methods are explicit, fast, and increase reproducibility. Arbitrary scoring, however, leads to questionable validity. As well, SDAs are not flexible enough to deal with complex cases because they cannot handle missing information and multiple possible drug and nondrug causes in a coherent way.[10,11]

The shortcomings found with SDAs were addressed by using a Bayesian method to evaluate the causal relationship between a drug and an adverse event.[11] The Bayesian Adverse Reaction Diagnostic Instrument (BARDI) is explicit in the information that is used and how each piece of information is weighted and uses Bayesian statistics to combine factors coherently.[11] The Bayesian method can include any relevant information and can consider multiple possible causes. Testing has shown that BARDI is valid.[12,13] This method is not used by clinicians very frequently, however, because of its apparent complexity and the extensive calculations involved.

This report describes a prototype computer program called MacBARDI-Q&A, which is a Bayesian-based diagnostic aid for hypersensitivity rashes, developed to facilitate the clinical use of BARDI. The method is compared with similar available approaches.

METHODS

BARDI

MacBARDI-Q&A is derived from the noncomputerized method of causality assessment called BARDI, which is used to calculate the odds in favor of a particular drug causing an adverse event compared with an alternative cause. These odds are referred to as the *posterior odds*.[11] The posterior odds factor is calculated by considering six assessment subsets: one deals with background epidemiologic or clinical trials information (the prior odds) and the other five deal with case specific information (the likelihood ratios). The prior odds (PrO) factor is the ratio of the expected drug-attributable risk and the background risk of a certain adverse event in a population sharing basic characteristics with the patient being considered (such as medical condition). The five likelihood ratios (LRs) deal with any information of differential diagnostic value under the categories of patient history (Hi); timing of the adverse event with respect to drug administration (Ti); characteristics of the adverse event (Ch); drug dechallenge (De), which refers to any signs, symptoms, or occurrences after drug withdrawal; and drug rechallenge (Re) or readministration of the suspected causal drug(s). The product of these factors is the posterior odds (PsO):

$$PsO = PrO \times LR(Hi) \times LR(Ti) \times LR(Ch) \times LR(De) \times LR(Re)$$

MacBARDI Spreadsheet

MacBARDI-Q&A is based on an earlier computerized spreadsheet that assessed cases of neutropenia suggested as being drug induced.[14-16] This spreadsheet (MacBARDI) also has been used for cases of Guillain-Barré syndrome associated with zimeldine,[17] pulmonary fibrosis associated with antiarrhythmics,[18] cutaneous reactions associated with sulfonamides,[19] and anticonvulsants,[13] fetal alcohol syndrome[20] and benzodiazepine withdrawal.[21]

The MacBARDI computerized spreadsheet contains or requires five types of information: (1) pure information lines that describe the input needed; (2) input lines that are the parameters used to calculate each of the six factors; (3) assumption lines, which are built-in inputs used in the calculations (i.e., assumptions); (4) calculation lines that calculate and show the value of each term in the assessment; and (5) output lines, which show the value of each factor necessary to calculate the posterior odds and the posterior odds itself.[14] MacBARDI facilitates updating case analyses as new information becomes available, has all the criteria necessary for a good causality assessment method (e.g., explicitness, flexibility), encourages learning and modeling, and substantially decreases the time required to assess cases.[14] Using the spreadsheet required knowledge of BARDI, however, and it did not have automatic database lookup, meaning the assessor had to find relevant information on the database and enter it on the spreadsheet.

Some of these limitations were corrected in MacBARDI-Q&A as described below.

RESULTS

MacBARDI-Q&A

MacBARDI-Q&A is a user-friendly diagnostic aid with a question and answer format. This program provides direct access to specifically prepared databases and provides a list of assumptions to allow the user to judge the medical and pharmacologic information on which the calculations are based. The program has three components: the interface (Q&A), the spreadsheet (MacBARDI) and a database of pertinent information (Q&A knowledge base) (Figure 1). The spreadsheet used was Microsoft Excel version 3.0 (Microsoft Corporation 1990, 1991). The program runs on a Macintosh II or any Macintosh with a minimum of 1 megabyte of random access memory (e.g., Macintosh SE). This program improves interaction with the computer compared with the MacBARDI spreadsheet alone by asking the user case-specific questions, using the response to look up appropriate information on the Q&A knowledgebase, inputting the information into the MacBARDI spreadsheet where calculations then are performed, and returning results to the assessor (Figure 1).

The prototype program has been developed for hypersensitivity skin reactions associated with sulfonamides and aromatic anticonvulsants (carbamazepine, phenobarbital, and phenytoin).[22] The Q&A knowledge base is a collection of epidemiologic, medical, and pharmacologic information regarding hypersensitivity skin reactions that has been specially encoded in a database. This knowledge base is based on published cases and expert opinion as outlined in an assumption list that is part of the program. The Q&A knowledge base provides information to the MacBARDI spreadsheet on drug- and nondrug-attributable risks of hypersensitivity rashes of different types; the magnitude of risk factors in the patient's history; the expected time of onset of both drug-induced and nondrug-induced reactions over the period the patient is at risk (i.e., time of onset distribution); the increase in likelihood of a certain cause for any characteristics of differential diagnosis value; and any changes in likelihood for certain dechallenge and rechallenge information. The assumption list can be accessed on screen or by printing out a hard copy. Both the assumption lists and knowledge base are updated as needed. For example, when a patient has taken a concomitant drug that is not in the knowledge base, this information can be obtained in a literature search and added to the database.

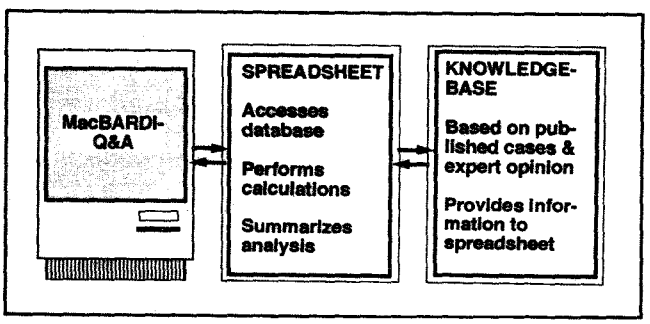

Figure 1. The three components of MacBARDI-Q&A.

Figure 2 shows the first four screens of an actual MacBARDI-Q&A printout where a prior odds was calculated. As can be seen, for each input required (designated by an arrow) such as the adverse event experienced and the drug the patient was taking, the program asks the relevant question and suggests possible answers. These possible answers (with the exception of "other") correspond to the information available in the Q&A knowledge base. For example, in this case, the patient experienced an exanthematous eruption (EE) while taking or shortly after a course of sulfonamides (D1). MacBARDI-Q&A uses these two pieces of information, accesses the Q&A knowledge base, and reports back that for a typical patient with an exanthematous eruption after taking a sulfonamide, the risk of a sulfonamide-induced rash is 1.5% and the background risk is 1.0%. Furthermore, the MacBARDI spreadsheet calculates that the prior odds is 1.5:1 in favor of the sulfonamide. This corresponds to a probability of 60% in favor of the sulfonamide and 40% in favor of alternative causes (Figure 2).

The assumption list shows that the incidence of sulfonamide-induced exanthematous eruptions was based on the midpoint of four studies with a range of 1 to 2%.[23–26] Using available estimates of the total incidence of rashes (i.e., drug plus nondrug, no attribution of cause done), which range from 2.1% to 2.4%[23,27] and average 2.3%, and subtracting the sulfonamide-attributable risks (1.5% as before), the nondrug risk of EE is approximately 1%. Subsequent factors, the likelihood ratios, are calculated in similar screens by giving an explanation of the input needed, reporting back the effect of each input, and then calculating and reporting the likelihood ratio. There are 10 to 20 case-specific questions that are asked as appropriate.

The user can verify how calculations were made by printing out the MacBARDI spreadsheet. The impact of missing or new information (sensitivity analy-

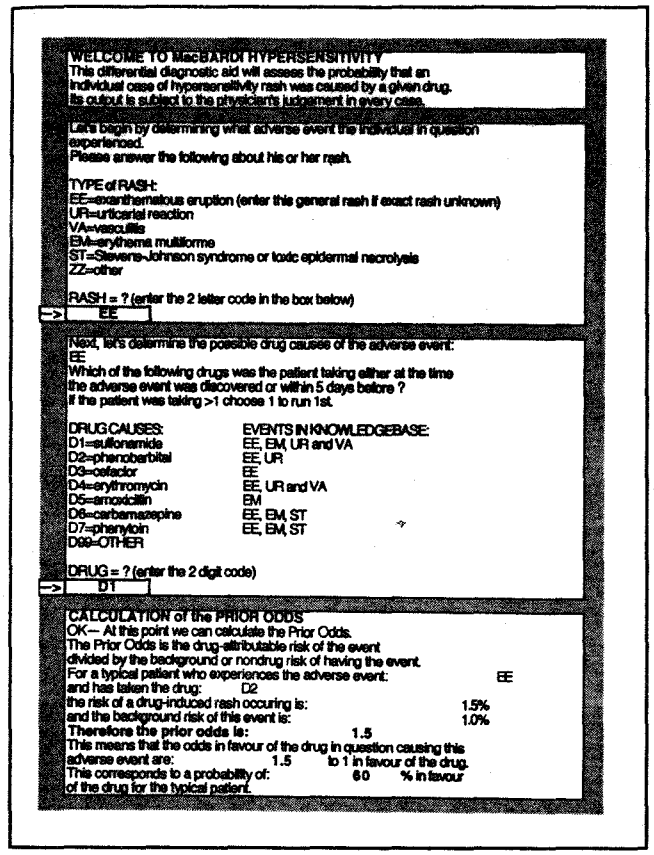

Figure 2. Actual printout from MacBARDI-Q&A.

sis) also can be assessed by repeating the calculations with relevant parameters changed and comparing results. As with BARDI, this Bayesian system has the ability to consider multiple possible drugs as causes. The drug causes are run through the program one by one and then the program gives an adjusted posterior probability to consider all drugs the patient was taking.

Cross Validation

MacBARDI-Q&A was cross-validated by comparing results with those of an *in vitro* rechallenge test, the lymphocyte toxicity assay.[28] The lymphocyte toxicity assay (LTA) was developed for anticonvulsant drugs[29,30] and subsequently expanded to include sulfonamides[31,32] and sorbinil.[33] This *in vitro* test is based on the hypothesis that a genetic defect in the detoxification of toxic drug metabolites is responsible for idiosyncratic adverse drug reactions such as multisystemic hypersensitivity reactions. When peripheral blood lymphocytes from patients are incubated with the drug and drug-metabolizing enzymes, some patients show an increase in percent dead cells of more than three standard deviations above the average for controls. This is interpreted as a decrease in the ability to detoxify the oxidative metabolites (which cause cell damage) compared with controls.[34] When MacBARDI-Q&A was tested on 27 cases of skin reactions associated with sulfonamide therapy, it showed 18 adverse events were associated with sulfonamide use (PsP = .61–.99) and 9 adverse events were not (PsP = .003–.47). Results were compared with a blindly and independently performed LTA and showed high concordance (96%) indicating cross-validity.[28]

DISCUSSION

The concomitant development of computerized diagnostic systems for clinical diagnosis and the theoretical framework for the causality assessment of ADRs have made possible the development of prototype computer programs such as MacBARBI-Q&A for the diagnosis of ADRs based on statistical methods. There are several reasons why these efforts may be useful. Firstly, the shortcomings of unaided clinical diagnosis have been recognized. The human mind has a limited ability to process many factors simultaneously.[35] Algorithms, although quickly learned and used, are too simplistic and inflexible because of their preset questions to deal with all the problems and complications encountered in the field of adverse reactions. Conversely, the longer more complex methods (such as the Bayesian-based approach) attain flexibility, wider applicability, and validity at the expense of ease of use and learning. Thus, a potential solution could be achieved by computerizing a longer, more complex method with demonstrated validity to decrease complexity for the user and time involved. This could favorably decrease the cost–benefit ratio.

Computerized methods for the diagnosis of ADRs also might be expected to decrease the incidence of errors associated with using diagnostic aids, force assessors to be more consistent in their assessments, and improve accessibility to those methods that are difficult to learn. Users also can be trained to diagnose adverse drug reactions using profile cases and being given feedback. Computers also have the potential to be linked with drug information databases. Thus, one can envision many potential benefits of a fully developed computer program to help diagnose ADRs.

MacBARDI-Q&A and its predecessor MacBARDI[14] are examples of some of the several prototype programs for diagnosing ADRs that have been developed recently (Table). A Bayesian-based computer-aided model also has been developed for prediction of risk

TABLE

Prototype Programs Developed for Computer-Aided Assessment of Adverse Drug Events

Program*	Type	Uses (Adverse Event/Drug(s))	Comment
MacBARDI	Bayesian spreadsheet	Neutropenia/antiarrhythmics Guillain-Barré syndrome/zimeldine Cutaneous reactions/sulfonamides Hypersensitivity reactions/anticonvulsants Pulmonary fibrosis/antiarrhythmics Fetal alcohol syndrome/ethanol Drug withdrawal reactions/benzodiazepines	Upgraded
Risk of allergic/pseudoallergic reactions	Bayesian model	Allergic and pseudoallergic reactions/plasma substitutes	Developed
Pseudomembranous Colitis I	Bayesian spreadsheet	Pseudomembranous colitis/antibiotics	Upgraded
Pseudomembranous Colitis II	Bayesian expert	Pseudomembranous colitis/antibiotics	In development
MacBARDI-Q&A	Bayesian expert	Cutaneous reactions/sulfonamides and anticonvulsants	In development

* *See text for references.*

for pseudoallergic reactions and histamine release in patients undergoing anesthesia and surgery.[36] This system was able to predict 86% of the patients who had a systemic reaction to plasma substitute, although prediction accuracy of cutaneous reactions and no reaction was poor compared with clinical diagnosis.[36]

A second example of a computerized diagnostic aid has been developed for cases of pseudomembranous colitis.[37] Like MacBARDI, this system began as a spreadsheet-based system[37] and was improved by developing an expert system that automatically makes the required estimates.[38] The expert system is useful because the component probabilities or likelihoods are difficult for the user to estimate and may depend on expertise the user does not possess. This prototype expert system has been tested on pseudomembraneous colitis associated with antibiotic use. The authors believe, however, that the current system is limited because it cannot deal with more than two drugs, does not consider the actual findings observed that led to a diagnosis of colitis, and does not consider interactions between antibiotics.[38] Nevertheless, it is an interesting demonstration of the use of expert systems for the causality assessment of adverse drug reactions, and such an approach has the potential to make efficient and valid assessments of the cause of suggested ADRs.

Thus, at least three systems have been developed for the computer-aided assessment of ADEs (Table). Although these systems are prototypes, they do provide an excellent demonstration of what might be possible using this methodology. Each system uses pharmacologic and medical information and medical expertise to assemble a knowledge base of information for evaluating cases of suspected ADRs. This allows assessors with varied expertise easy access to the required information. The Bayesian systems are rapid, and allow the user to arrive at results that would be difficult to obtain using clinical judgment alone. Each system uses a coherent inferential basis and consistently gives the same assessment given the same clinical information.

In summary, our report has illustrated a new computerized Bayesian-based system for diagnosing hypersensitivity reactions (MacBARBI-Q&A). This system represents an advance over the MacBARDI spreadsheet because of improved user friendliness, automatic access to specially prepared databases, and because it has been cross-validated to another diagnostic test. Experience with other computerized diagnostic aids, however, indicates that a useful system for computer-aided diagnosis must meet several requirements including: use in an area of perceived need; an appropriate underlying basis; answer justification; an evaluation of accuracy; adaptability for use in different areas (e.g., systems are sometimes dependent on in-house studies or a limited number of experts); practical needs (e.g., cost, ease of use); and extensive medical and pharmacologic databases.[4] As yet, the prototype programs are lacking in adaptability, and have incorporated limited medical and pharmacologic databases. As well, only MacBARDI-Q&A has had an evaluation of accuracy using cross-validation by comparison with another diagnostic test. The need for a method of accurate and fast causality assessment exists, however, and the results so far are promising.

MacBARDI-Q&A and the existing programs require further development: finite tasks should be

identified, and programs should be expanded and tested in a variety of situations. Systematic testing of MacBARDI-Q&A for hypersensitivity reactions and other putative ADRs (such as pancreatitis, blood dyscrasias, and withdrawal reactions) is underway. Given the advantages such systems would have, their continued development could improve the causality assessment of adverse drug events.

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