

Drug Interactions Software Programs

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The value of a computer application is usually dependent on the program's ability to store, rearrange, and retrieve information in a format that is useful to the computer user. Based on a list of drugs (input), drug interactions programs search their databases for possible interactions between each drug pair in the input list. An output list specifies pairs of drugs that potentially interact. Since each program uses its own information database, results may differ slightly among programs. In general, however, the screen menus, appearance of the programs, and the "extras" included in each program differ more than the programs' drug interactions output. The software programs tested are all easy to use.

Each of the three drug interactions programs re-

viewed has unique features that may appeal to certain users. *The Medical Letter Drug Interactions Program* is the least costly and provides the most academic output, allowing users to view citations for each specific interaction. The *PDR Drug Interactions and Side Effects* software includes a side effects index that allows either searching of a drug, which produces a list of the drug's side effects, or searching of a specific side effect, which produces a list of drugs associated with that side effect. *Drug Interactions III* is the only program that allows users to add drug interactions to its database.

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Computer applications in medicine may be divided into two major categories: administrative uses and clinical uses. Many family physicians are familiar with administrative uses, such as billing and accounts receivable management. The American Academy of Family Physicians has developed a manual to guide its members in administrative uses of computers.¹

The rationale for computerization of any task is that the computer, in some fashion, facilitates the user's ability to perform a task. Storage of information, with retrieval based on specific user needs, is one of the tasks for which computers are ideal.

The common thread among computer applications, then, is the ability a program gives a computer to store, rearrange, and retrieve information. Basic categories of computer software programs include word processing programs, communications programs, spreadsheet programs, and database programs. Word processing programs are designed specifically to facilitate storage, retrieval, manipulation, and printing of words. Communications software programs allow transmission of infor-

mation between computers at different sites, often by telephone lines. An example is GRATEFUL MED, a specific communications program that allows users access to the National Library of Medicine's (NLM) databases through any computer-compatible telephone line. (This process has previously been reviewed in the Journal.²) A spreadsheet program, the computer equivalent of a large accounting-type work sheet, allows manipulation of columns and rows of data, usually primarily numerical. A database program consists of data stored in "records," where each record contains similar types of data, and from which information can be extracted and manipulated. Because these programs are designed to perform tasks on large amounts of data, databases are suited to many clinical applications. A telephone book would be an example of a noncomputerized database, with each listing comprising one record. Most physicians are familiar with the NLM databases of literature citations, at least through requesting literature searches from their librarians. Databases that accept input of symptoms and signs and provide output of possible diagnoses have been developed and are now commercially available.³ Drug interactions programs are specialized database applications.

The current clinical utility of drug interactions programs is apparent, and their utility certainly will increase because the number of patients on multi-drug regimens

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Table 1. Basic Features of Three Drug Interactions Programs

Feature	<i>PDR Drug Interactions and Side Effects (PDR)</i>	<i>Drug Interactions III (DI-III)</i>	<i>Drug Interactions Program (DIP)</i>
Version/date	3.0 (1991)	3.3 (1990)	Issue 4 (September 1990)
Price	\$159; with optional "Indications" index, \$219	\$189	\$60; \$100 for program plus 2 updates
Updates	\$199 for 3 per year; \$89 for January 1992 update	Annual	Approximately every 8 months
Distributor address (phone number)	Medical Economics Company Oradell, NJ 07649 (201-262-3030)	Quaker State Software, Inc. 4600 Custer Drive, Harrisburg, PA 17110 (717-657-2595)	The Medical Letter 1000 Main Street, New Rochelle, NY 10801 (914-235-0500)
How supplied	5 360K (5-1/4"), 3 720K (3-1/2") or 2 high-density diskettes	1 720K (3-1/2") or 2 360K (5-1/4") diskettes	1 720K (3-1/2") or 2 360K (5-1/4") diskettes
Documentation	48-page paperback booklet	Loose-leaf notebook	21-page paperback booklet
Hardware requirements	IBM PC or compatible microcomputer; DOS 3.1 or higher, 512K RAM, hard drive with 1.6M free storage space	IBM PC or compatible microcomputer; DOS 2.1 or higher	IBM PC or compatible microcomputer; 256 RAM; DOS 2.1 or higher
Mouse support	No	No	No
Customer support	Toll-free telephone	Toll-call	None specified
Demonstration disks	No	No	No
Money back guarantee	10 day	30 day	30 day

is likely to increase.⁴ The number of conditions amenable to drug therapy is increasing, with the advent of new antiviral agents and effective therapy for obsessive-compulsive disorder, for example. The number of drugs available to treat each condition is increasing, with new drugs often added to the regimens rather than replacing previous agents, such as the addition of selegiline hydrochloride to Parkinson's disease regimens and the addition of angiotensin-converting enzyme inhibitors to congestive heart failure regimens. Additionally, the population is aging,⁵ and the elderly consume more drugs per capita.⁶⁻⁸

It is easy for patients to accumulate long medication lists. Certain antibiotics, pain medications, and symptom relievers for colds, for example, are often prescribed in combination, allowing the number of individual medications taken to reach high numbers quickly. Prescribing trimethoprim-sulfamethoxazole, acetaminophen with codeine, and an antihistamine-decongestant for a patient with sinusitis provides six systemic drugs. Most primary care physicians are familiar with these common combinations. However, they may be unfamiliar with drug interactions among medications that they prescribe infrequently or that are prescribed by consultants. The problem is obviously compounded if the patient is already being treated with antihypertensive medications, or with lithium or carbamazepine, or with some combination of these drugs. When patients are taking multiple medications, it may be an onerous if not an impossible task to

manually ascertain whether clinically significant interactions are likely among the medications. With six drugs, there are 15 unique two-drug combinations and with 10 drugs, 45 unique two-drug combinations. Within seconds, a computer can analyze these combinations for interactions.

Therefore, in my opinion, for the physician with computer access, the question is not whether one should have a drug interactions program, but which one. We reviewed three drug interactions programs that automate the task of identifying interactions among up to 20 simultaneous medications. Basic information about the programs is presented in Table 1.

General Features and Similarities

The drug interactions programs were evaluated on a variety of hardware (Compaq, IBM, IBM compatible) with various displays (LCD, monochrome, color). No major difficulties were noted. All systems were easy to install. Manuals were short; the pertinent information was clear. A purchaser with modest computer familiarity would be able to learn any of the three programs within 5 to 10 minutes. None of the programs allowed memory-resident installation and none allowed significant user customization. The basic features of these programs were similar and are described in this section. Some of the

Table 2. Differences Among Drug Interaction Programs*

	PDR	DIP	DI-III
Screen and menu design	Good	Satisfactory	Good
Drug-food interaction option	Yes	Limited	Yes
Alcohol/ethanol-drug interaction option	No	Yes	Yes
Option to write output to data file	Yes	Yes	No
Option for user to add drug interactions	No	No	Yes
Specific references for each interaction	No	Yes	No
Specific advice about each interaction	No	Yes	No
Side effects index or information	Yes	No	Limited
List contains Robitussin-DM brand name	Yes	No	No
Accepts informal input (eg, "HCTZ")	No	No	Yes
Allows drugs not in database to be placed on patient's drug list	No	Yes	Yes
Flagged drug pairs in sample drug list†	12	14	9
Exclusive interactions from sample list†	3	5	1
Interactions exclusively omitted from sample drug list†	0	1	2

*Programs: PDR, *PDR Drug Interactions and Side Effects*; DIP, *Drug Interactions Program*; DI-III, *Drug Interactions III*.

†An eight-drug list (Table 3) was entered into each program. Of 28 possible drug-interaction pairs, 18 pairs were flagged by one or more programs. The number of pairs that each program flagged is presented, as well as the number of pairs flagged exclusively by each program and omitted exclusively by each program.

differences in features are collated in Table 2 and discussed in the descriptions of the individual programs.

Each program is menu-driven, providing prompts and choices. All programs are sufficiently intuitive to allow use with minimal reliance on the manuals. All programs allow input of 2 to 20 drugs, which are then searched for potential interactions. Interacting drugs are listed in pairs along with nature and consequences of the interactions. Drug lists may be saved, recalled, modified, and rerun. Drug lists (input) and interaction lists (output) may be printed, allowing an assistant to use the program and to provide the printed results to the physician. Each program allows searching of its database to produce a list of drugs that interact with a single user-specified drug. All systems provide some method of spelling assistance and of verifying that entered drugs were in its database. Entry of drug lists differ among programs, but all methods were acceptable. When the interactions identified by the programs (Tables 2 and 3) are tabulated, more similarities than differences are apparent.

Each of these three programs uses its own unique database. This situation is unlike MEDLINE and its related files, which are one set of databases maintained by NLM and distributed to multiple vendors. In literature searching, the search processes differ by vendor, but the results

Table 3. Interactions Identified by the Three Programs*

Drug List (Input)	Interaction List (Output)						
	Ibuprofen	Aspirin	Warfarin	Digoxin	Verapamil	Propranolol	Haloperidol
Lithium	PDR DIP DI-III	—	—	—	DIP	—	PDR DIP DI-III
Haloperidol	DIP	—	PDR	—	PDR	PDR DIP	—
Propranolol	PDR	DI-III	DIP	PDR DI-III	PDR DIP DI-III	—	—
Verapamil	—	DIP	—	PDR DIP DI-III	—	—	—
Digoxin	DIP	—	—	—	—	—	—
Warfarin	PDR DIP DI-III	PDR	—	—	—	—	—
Aspirin	PDR DIP DI-III	—	—	—	—	—	—

*Programs: PDR, *PDR Drug Interactions and Side Effects*; DIP, *Drug Interactions Program*; DI-III, *Drug Interactions III*

Note: The eight drugs in this table, providing 28 conceivable interaction pairs, were entered into each drug interaction program. If a program flagged potential interactions between two drugs, the program's name appears in the cell formed by the intersection of one drug's row with the other drug's column. For example, all three programs flagged ibuprofen plus aspirin, whereas only DIP flagged digoxin and ibuprofen. All three programs concurred on seven positive interaction pairs and 10 pairs with an absence of detected interactions. Of the remaining 11 pairs, eight pairs were listed by only one program and three pairs were listed by two of the three programs.

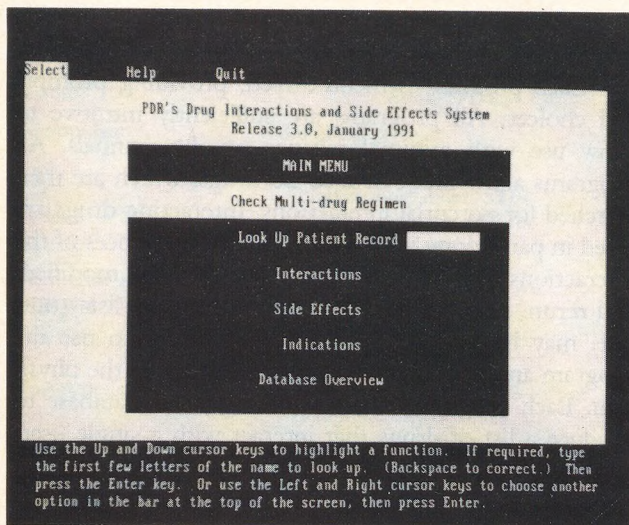


Figure 1. Initial menu screen for the PDR program. The right and left cursor keys are used to select among the horizontal menu choices along the top of the screen, and the up and down cursor keys are used to select among the vertical choices.

should theoretically be the same. For drug interactions programs, the search processes are uncomplicated; thus, the emphasis should be placed on the comprehensiveness and clinical relevance of the output.

Individual Programs

PDR Drug Interactions and Side Effects (PDR)

Of the three programs, PDR has the most professional feel. It includes citations for every fully described product in PDR and its ophthalmological and nonprescription companion volumes. However, its database is entirely derived from the product descriptions submitted for publication in the *Physicians' Desk Reference*. Entry into the program delivers the user to the main menu. This large vertical menu offers options of Check Multi-drug Regimen, Look Up Patient Record, Interactions, Side Effects, Indications, and Database Overview (Figure 1). Options are selected by pointing with the cursor keys and selecting with the Enter key. Submenus appear when needed and on-screen instruction is provided whether needed or not. Figure 2 illustrates the display for initiating an interactions search.

Unlike the other programs, the instructions for PDR suggest that only the first several letters of a drug name be entered. Thereafter, the program presents options that match those letters, from which the user chooses by pointing with the cursor and selecting with the Enter key. For example, to enter amoxicillin, the user

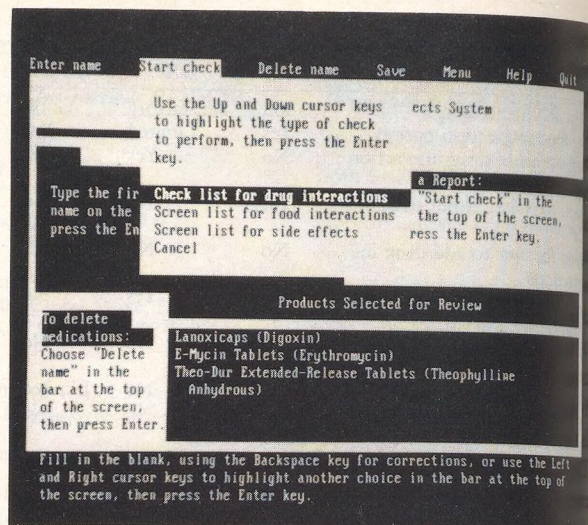


Figure 2. Screen for initiating drug interactions search in the PDR program. Drug names have been entered; note that only brand-name searching is permissible. Horizontal cursor keys are used to choose among the options along the horizontal menu at the top of the screen. Vertical cursor keys are used to select among the vertical menu options; "check list for drug interactions" is currently highlighted and would be chosen by pressing the Enter key.

may type "amo" and press Enter. PDR responds by offering choices of amoxapine, amoxicillin, and two listings for Amoxil (adult and pediatric formulations). If the user chooses amoxicillin, another box of choices appears, this one offering two Amoxil, one Augmentin, and two Trimox choices, plus a message that begins: "The PDR System works with specific brands rather than generic overviews."

Unfortunately, choosing different brands of the same generic product may produce different results. For example, among brand-name aspirin products, listings for Easprin, Ecotrin, and Norwich extra-strength aspirin differ substantially. Interactions listed for Easprin include alcohol, corticosteroid preparations, glipizide, glyburide, chlorpropamide, heparin, warfarin, and insulin. For Norwich aspirin, listed interactions include numerous nonsteroidal anti-inflammatory agents, none of which are listed under Easpirin. The Ecotrin listing contains no mention of alcohol, corticosteroid or nonsteroidal preparations, glipizide, or the other drugs mentioned above.

Two PDR features not available with the other programs are the Side Effects function and the Indications index. The Indications index is optional; at the time of this writing, it cost \$60 more than the same software without this feature.

If the Side Effects option is selected, the user is presented the choice of two entry blanks, one for a drug

and the other for a side effect. Entering a brand name product in the drug entry area elicits the *Physicians' Desk Reference* list of side effects associated with that drug. (If a generic drug name is entered, a list of corresponding brand names is presented; the user must choose one before the program will proceed.) Entering a side effect on the appropriate line produces a list of drugs that, according to the *Physicians' Desk Reference*, are associated with that specific side effect. For example, selecting the drug option and entering Augmentin will produce a list of the adverse reactions for this product that are discussed in the *Physicians' Desk Reference*. Selecting the Symptom option and entering "impotence" produces a list of brand name drugs associated with this side effect. The Indications option functions identically, allowing entry of a drug name or an indication. For example, to produce a list of drugs officially labeled for use in urinary tract infections, entering the letters "urin" produces a list of options, including "urinary bladder, reflex neurogenic, symptomatic relief of"; "infections, urinary tract"; "pain, urinary tract"; "urine, acidification of"; and so on. The appropriate line is highlighted using cursor keys and selected with the Enter key. Because PDR uses a brand-name system, a few extra but swift and easy cursor and keystrokes are needed to translate generic entries. However, this inefficiency is mitigated by requiring only the first few characters for any entry. Entry screens are good and program responses are swift and logical in all options.

PDR has some additional drawbacks. The user may not add a drug to the medication list that PDR cannot find in its database. The other programs, *Drug Interactions III* and the *Drugs Interaction Program*, allow this addition so that the user may store a patient's complete medication list. Alcohol (or ethanol) cannot be added to a list, and I could not find a mechanism for detecting drug-ethanol interactions. (Each drug could be searched individually to see whether the *Physicians' Desk Reference* information mentioned an interaction of the drug with alcohol, but that would be an inefficient use of the computer's capability and the user's time.) Also, because much of the screen contains instructions, only a small screen window remains for viewing pertinent retrievals. For example, the extensive list of drugs that interact with warfarin must be viewed through an eight-line window. There were virtually no user-definable options, such as adjusting print options, sound, and screen windows, or obliterating the screen-cluttering instructions. Although these points may sound picky, PDR produces a loud, high-pitched screech if the user tries to cursor past the beginning or the end of a list. Furthermore, it provides one screech for every extra key stroke, which may be a considerable annoyance in certain surroundings. The

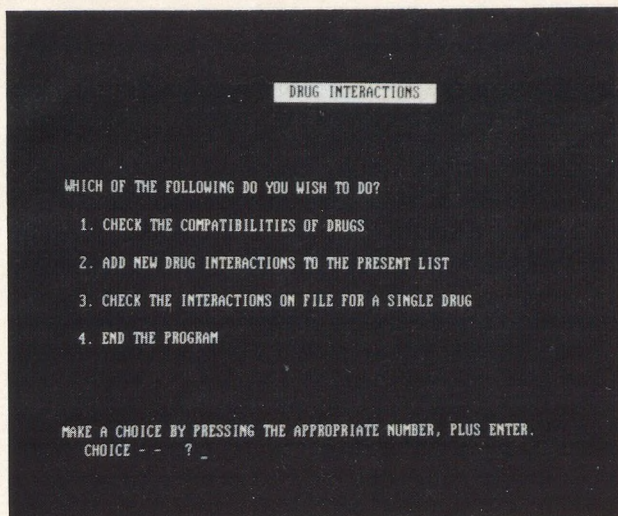


Figure 3. Initial menu screen for the DI-III program. As indicated on the screen, the user must choose the number plus press Enter.

program's inability to set print options negates some otherwise potentially useful features. For example, attempting to produce a printed list of drugs that interact with warfarin, brand-name output cannot be suppressed, producing pages of brand-name aspirin-containing drugs, chlorpheniramine-containing drugs, and so on. If the user could copy the information onto a disk, the user could modify it with a word processor, but the output list is too large for PDR to copy onto a disk, nullifying this potential alternative.

Drug Interactions III (DI-III)

DI-III is a compiled BASIC program that runs noticeably slower than the other programs, but is functional when run on a 80286-based computer. Unlike PDR, DI-III does not physically require a hard disk; however, I would not recommend trying this program with older equipment or from a floppy disk drive. Presumably the product of a small company, the update frequency of this product might be less predictable than for the other two programs.

The DI-III database is derived from the *Physicians' Desk Reference*, *Drug Interaction Facts: Facts and Comparisons*, *The Medical Letter Handbook of Drug Interactions*, and eight other sources. Unlike the other products, this is the only product that allows users to add new drug interactions to its database. The addition process could be simplified; in its current form, it would intimidate most computer novices. It is initiated by choosing an option on the main menu (Figure 3), but the process is


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ENTER THE FOLLOWING INFORMATION IN CAPITAL LETTERS

WHAT IS THE PATIENT'S NAME?          GARY FOX

LIST ALL OF THE DRUGS GARY FOX IS CURRENTLY TAKING.
USE EITHER THE GENERIC NAME OR THE MOST COMMON BRAND
NAME OF EACH DRUG. SPACE IS PROVIDED TO LIST UP TO
TWENTY DIFFERENT MEDICATIONS.

IF DRUG NAME IS MORE THAN ONE WORD, THEN ONE SPACE BETWEEN WORDS,
UNLESS WORDS ARE JOINED BY A HYPHEN OR OTHER CHARACTER.

AFTER YOU HAVE ENTERED THE LAST DRUG IN GARY FOX'S
LIST, THEN ENTER 'F' (for FINISH) .

LIST DRUG No. 1          ? DIGOXIN
LIST DRUG No. 2          ? ERYTHROMYCIN
LIST DRUG No. 3          ? THEOPHYLLINE
LIST DRUG No. 4          ? F_

```

Figure 4. Data entry screen for the DI-III program. Entering the patient's name is optional. If entered, it appears on print-outs. After all drugs are entered, the user types "F" to indicate the list is finished. The other two programs check spelling when each drug is entered. In DI-III, spelling is checked after the list is completed.

not entirely menu-driven. Additionally, DI-III accepts common clinical abbreviations such as "asa," "fc," "k," and "hctz." "Food," "sun," "alcohol," and "smoking" may be added to a drug list for interaction searching (Figure 4). A list may be checked for drugs that may contribute to sexual dysfunction by adding "sex" to the list. (PDR allows retrieval of this information through the Side Effects index.) This program lists only six drugs that produce photosensitivity reactions, with neither tetracycline or sulfonamides being among them, leading to a question about the reliability of this function. There is no menu function or "help" function that allows these ancillary terms to be recalled; they must be memorized or retrieved from the manual.

DI-III does not allow experienced users to bypass the introductory screen and instruction prompts. A few unnecessary keystrokes are required; for example, the Enter key must be pressed after each menu choice (Figure 4) and screen prompt. No default values are offered to speed entry. There is no set-up feature that allows the user to select options, except for a color display option. Unlike the other two programs, DI-III does not allow its output, the drug interaction list, to be copied onto a disk file. (Of course, it may be viewed on the monitor or printed.)

Drug Interactions Program (DIP)

Unlike DI-III, DIP performs efficiently on an antique 8088-based computer with a single floppy disk drive.

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Drug Interaction Program

Main Menu

1 Enter drug names into Current Drug List
2 Search for interactions between drugs in Current Drug List
3 List drugs that interact with a single drug
4 Browse the index of drugs
5 Print or clear Current Drug List
6 Retrieve, save, or delete a drug list file
7 Display references listed in drug interactions
8 Instructions

Enter a number 1-8 or 'q' to quit:

```

Figure 5. Initial menu screen for DIP program. At the termination of each function, this menu reappears. The DIP programmers provide an option to directly invoke the drug entry screen. This "quick" option must be selected at the DOS prompt. Options 3 through 8 are unavailable when the "quick" option is selected.

(However, in such an arrangement, switching of disks is necessary.) Like DI-III, DIP has a homespun look and feel that is apparent from the start: The menu (Figure 5) is an unwieldy and unsightly one consisting of eight items (plus "q" for quit), with a median of 6.5 words per item (compared with the PDR median of 2). Default options are not provided and menu branching has not been optimized. For example, after entry of a drug list, the user is returned to the wordy main menu rather than a submenu of the most likely subsequent choices. However, the DIP developers provided an option, which can be invoked when loading the program from the DOS prompt, that provides direct access to the drug entry screen. After the drug list is entered, the drug interactions are displayed on the screen without going through any additional menus. However, no method was found for returning to the main program menu when the program was invoked in this manner. Therefore, without exiting the program, reinvoking it in the normal mode, and reentering the drug list, there were no methods for saving the drug list (the input), printing, saving the interactions list (the output), or using the other features available from the main menu. Also, in the "quick" mode, the user is unable to check interactions associated with a single drug.

Unlike DI-III, DIP requires pressing only the appropriate menu number or single-letter response to prompts, without requiring confirmation with the Enter key. If an incorrect key is pressed, it is easy to return to

the main menu. On the other hand, DI-III forces the user to cycle through the entire program sequence before returning to the main menu.

DIP formats results in the most academic fashion of any of the programs. Only one drug interaction pair is listed on the screen at a time. Each interaction is followed by three additional categories of information. First, each of the adverse effects of the combination, along with the suspected mechanism, is listed. Second, comments and recommendations (such as monitoring drug levels or avoiding the combination altogether) are provided. Third, an option for listing the references specific to each interaction is provided. By pressing "y" (yes) or "n" (no) in response to a prompt, the user indicates whether he or she wishes to see the reference list for that specific interaction. An "n" response immediately produces the next drug pair for which an interaction was identified. The second and third features are unique among these programs. Unfortunately, the appearance of this output is suboptimal, often omitting grammatical and eye-pleasing spaces and punctuation.

Another unique and important feature is DIP's flagging of drugs recognized as belonging to the same class. For example, ibuprofen, naproxen, and diflunisal are listed as nonsteroidal agents, and appropriate messages appear when these agents are listed together. Aspirin, however, is listed as a salicylate, and no message appears when it is listed with the nonsteroidal agents. This class-detection feature was inconsistent: entering lists of four calcium channel blocking agents or three central alpha₂-receptor stimulating agents produced no warnings and retrieved no interactions. If the generic name and a brand name of the same drug are entered, the same-class-additive-effect warning generally appears, but even this feature is not foolproof: Bufferin (antacid plus aspirin) and aspirin are not flagged when presented together, and the three-drug combination of Septra (trimethoprim-sulfamethoxazole), trimethoprim, and sulmethoxazole shows no warnings and retrieves no interactions when they appear together. Surprisingly, DIP's database does not flag the potential propranolol-digoxin interaction or the carbamazepine-monomamine oxidase inhibitor interaction.

Unlike DI-III's quest to allow user-friendly input, DIP responds to such inputs as "theophylline," "tetracycline," and "erythromycin," with "Did you mean 'THEOPHYLLINES?'" and so on (Figure 6). "Tricyclic antidepressants" is not acceptable input; "antidepressants, tricyclic" is. Also, brand names of common drugs (eg, Glucotrol) are occasionally not recognized by the program. I could not find any feature that allowed printing the list of agents interacting with a single drug, although results of multi-drug searches may be printed.

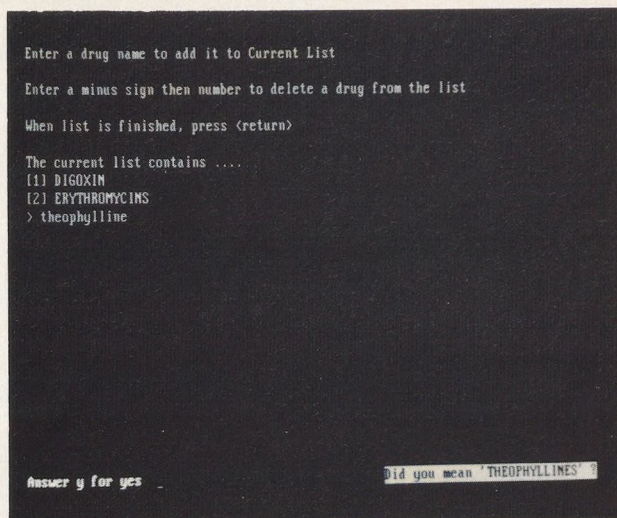


Figure 6. Data entry screen for the DIP program. Note that the program requires "erythromycins" and "theophyllines" for input; a prompt, illustrated on the screen, is provided if the user enters the singular name.

Conclusions

Each of these drug interactions software programs uses its own database. Each provides a different interface for the user to access the information in its database, but all are easy to learn and use. For use on an 80286-based computer with a hard drive, all are acceptable programs. Each of these programs has its idiosyncracies and none is a replacement for clinical wisdom. Each leaves specific areas for improvement and there are areas where all could use improvement, especially the incorporation of user set-up routines. PDR allows only brand name inputs and has only one source contributing to its database, but it has predictable updates and useful features not found in the other databases; these features may be the deciding factor for some users. DIP is the most academic of the three programs, the price is featherweight, it performs expeditiously, especially with the "quick" option, and it has a competitive 30-day free trial period. DI-III is a slower but functional, easy-to-use product that allows user additions, accepts common medical abbreviations, and allows retrieval of several drug-environmental interactions by allowing the addition of such items as "sun" to the drug list, a feature that all drug interaction programs should ideally possess.

Recognizing its frailties, for users who can overlook its glitzlessness, DIP is my recommendation. DIP is the only choice for impatient users owning 8088-based computers or machines without hard drives. If professional sparkle or the side effects and indications indices are priorities, and brand-name input is acceptable, choose

PDR. As the only product allowing user additions, DI-III should be considered by computerphiles wishing to make a one-time software purchase and to keep the database up to date themselves.

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