Third Edition

EDI 3

Evaluations of Drug Interactions

Arthur F. Shinn
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APhA Professional Drug Systems

Evaluations of Drug Interactions

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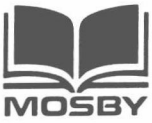

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Foreword

Health professionals know that pharmaceutical products often have a dramatic beneficial impact in patient care and treatment. Many times, drugs represent the crucial difference between life and death.

Health professionals also are acutely aware that pharmaceutical products can be "double-edged swords." They can be subject to abuse; they can deteriorate to toxic degradation products because of inherent instability; they can be taken in overdose; they can be taken at improper times or with incorrect frequency; they can cause severe allergic reactions; and so on.

Approximately 20 years ago, pharmacists and other health care practitioners began to recognize another drug-related problem. This new hazard came to be known or identified as "drug interactions"—a phenomenon in which a patient taking two drugs concurrently has a response that is significantly different from that which would have been anticipated from the two drugs individually.

The pharmacy profession was in the forefront in recognizing this new problem and in attempting to manage it. Pharmacists authored articles for pharmacy and medical publications in order to alert their colleagues to the problem. Also, individual pharmacists prepared charts and tabulations for their personal use in monitoring drugs prescribed for their patients. Some of these charts were reproduced for distribution to their fellow pharmacists. But the American Pharmaceutical Association (APhA) considered these well-intended efforts to fall short of the authoritative information that pharmacists needed to deal with this serious drug interaction problem.

Accordingly, APhA developed a solution embodying a unique approach: a reference book entitled *Evaluations of Drug Interactions* (EDI). Several things made EDI different from other available sources of drug interaction information, whether in chart form or in book form: (1) broadly based panels of experts were constituted to deal with each pharmacologic drug class, thereby providing both special expertise and a group consensus; (2) interactions were covered in monograph format with all related drugs appropriately discussed; (3) clinical significance was carefully weighed and described; (4) suggestions were offered as to alternate therapy or other suitable routes to best manage the interaction; (5) only carefully culled, original literature references were utilized and, after documentation, were cited in the monograph; and (6) for ease of identification, drug trade names were listed and cross referenced for all nonproprietary drug names in the monographs. APhA also enlisted the cooperation of related organizations of health care professionals and included on its panels individual experts from medicine, dentistry, nursing, and other areas of the health sciences.

The publication (EDI) was well received within pharmacy as well as by the health care community at large. APhA was gratified with the highly favorable reception and subsequently produced an extensive supplement, then an entirely new edition, and then a major supplement to that second edition.

But technology advanced in giant steps during those years, and the need to computerize the information in EDI became increasingly apparent—both for keeping the information database itself up-to-date and for efficient utilization at the user level. As a consequence, APhA sought out a potential partner with strong experience, know-how, and capabilities in the field of computerized drug information, as well as a serious commitment and dedication to maintaining the integrity and high standard of quality of APhA's EDI information base.

Such a partner was found in Professional Drug Systems, Inc. (PDS). Their willingness to establish and maintain the staff and outside consultant expertise needed to accomplish the task of producing a high-quality new edition of EDI was a crucial consideration from APhA's viewpoint. They have admirably met and even exceeded that commitment.

Indeed, they have brought into the partnership an added benefit. From PDS came a computerized database backed up with over 6 years of experience in the active practice of pharmacy. That database used EDI as a primary source of drug interaction information. In addition, it had been used to analyze several million prescription orders for hundreds of thousands of patients. This experience offered the background necessary for developing an information bank that combines a sophisticated, comprehensive database with a practical easy-to-use format that is readily adapted to most pharmacy practices.

For the past 2 years, PDS has worked diligently to update and expand EDI and to convert its resource information into forms and formats that would be convenient to use by pharmacists and other practitioners. APhA staff and an APhA appointed and administered Scientific Review Panel have closely monitored the efforts and products emanating from Professional Drug Systems' operation relative to the EDI database and to the software and hard-copy publications derived from the database.

On the basis of its monitoring and review activity, APhA is pleased to extend its full endorsement regarding the overall scientific quality of the technical content of these PDS produced products. Moreover, the APhA-PDS joint commitment is planned to be an on-going one, with future updates, supplements, and new editions all derived in a similar, carefully developed manner.

Before closing, APhA wishes to recognize the many, many people who collectively joined together in working to make and keep EDI a highly credible and invaluable resource. For EDI's third edition these people include the Professional Drug Systems' Contributors, the APhA Scientific Review Panel, and key scientific and professional staff people at PDS and APhA. Their names may be found elsewhere in this publication.

It is our fervent hope that this new EDI will play a significant part in helping to control the overall drug interaction problem and in reducing the level of those unfortunate deaths and hospitalizations.

John F. Schlegel, Pharm.D.
President
American Pharmaceutical Association

Acknowledgments

The preparation of the third edition of *Evaluations of Drug Interactions* could not have been possible without the efforts of many individuals. Space does not permit us to acknowledge each person separately. Nevertheless, we want to express our appreciation to all those who have helped in the development of this book, for without each one of them this publication would have been impossible.

We would especially like to express our appreciation to Mr. Stuart L. Bascomb, Chief Operating Officer of Professional Drug Systems, the late Dr. William S. Apple, Past President of APhA, and Dr. Norman A. Campbell, J.D., Ph.D., Professor of Pharmacy Administration, University of Rhode Island, whose work and perseverance lead to the relationship that allowed EDI-3 to be developed.

Special appreciation is also given to Dr. John F. Schlegel, APhA President, Dr. Edward G. Feldmann, APhA Vice President for Scientific Affairs, and Dr. Richard P. Penna, APhA Vice President for Professional Affairs, for their support, advice, and review of this publication. We would also like to acknowledge the individuals who worked with and for the APhA and were involved in the previous editions of EDI. In a very real sense, they set a foundation upon which we were able to develop this project.

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Arthur F. Shinn
Robert P. Shrewsbury

Introduction

There has been an increasing awareness of the possibility of drug interactions among health care practitioners. Because of the growing number of available drugs, both prescription and nonprescription, and the great amount of literature dealing with the subject, it is becoming increasingly difficult for the health care professional to effectively evaluate drug interactions. EDI provides the clinician a concise evaluation of the literature in a comprehensive, easy-to-use format.

A drug interaction is defined as occurring whenever the effects of one drug are modified in or on the body by the prior or concurrent administration of another pharmacologically active substance. Drug interactions included in this book are those that, when they occur, may result in an antagonistic, synergistic, or unexpected response.

All attempts have been made to include drug interactions that have occurred in humans. When necessary, supportive medical literature discussing animal or in vitro studies have been included to clarify mechanisms, related drugs, or the drug interactions themselves.

When evaluating the various drug interactions, one must address numerous considerations. Most interactions are quite complex and variable, depending on different "patient-specific parameters" such as disease states, weight, age, sex, and renal excretion. These parameters are certainly a concern to the health professional, and these patient variables need to be considered since they may further affect the drug interaction significance. It is important to remember that what is of minor clinical significance with one patient could be a major problem to another patient, and vice versa, if history applies (e.g., renal failure, hepatic function problems, duration of therapy).

The editors, consulting contributors, interdisciplinary review panel, and members from the MEDICOM™ consulting group have reviewed the known and pertinent medical documentation and developed a meaningful monograph for the user regarding each particular drug interaction. This group of professionals has analyzed each drug interaction monograph and has assigned a significance code (see User's Guide). This coding is intended to give an immediate and firsthand referencing guide to the particular drug interaction. The user may then combine the medical information in the monograph with his or her own professional judgment to develop a final decision and course of action. This third edition of *Evaluations of Drug Interactions* is to be considered as one tool available to a health care practitioner making a drug therapy decision and not as a substitute for professional judgment.

The contents of each chapter is divided into two sections: summary tables and detailed monographs.

The *summary tables* include a brief description of each individual drug interaction in a condensed tabular format. Included are statements of potential pharmacologic effects and recommendations as well as the significance code pertaining to that specific drug interaction. This section is intended to provide the user with a readily accessible, concise review of the drug interactions involving the therapeutic class of drugs pertinent to that chapter.

The *detailed monographs* are arranged as follows:

1. *Title of the Interacting Drugs by Generic Name.* The generic names of the drug interaction pair that appear in the title of the monograph relate to those agents that have the greatest degree of documentation in the medical literature and/or those that are most often used in clinical practice. Combinations like multiple metal ions found in antacid preparations are listed in the heading as a group of interacting agents when it is not ascertained in the literature which particular agents may be involved. Oral contraceptive agents are handled in a similar manner in that most dosage forms are in combination and assessment of the causative agent is difficult to document. Refer to the User's Guide for a discussion of chapter assignments and significance coding.
2. *Summary.* This pertains to the overall effect of the interaction.
3. *Related Drugs.* This section broadens the scope of the monograph and includes a discussion of those agents that are either pharmacologically, pharmacokinetically, or chemically related to either of the drugs appearing in the monograph title. If any of these related agents is specifically implicated by the mechanism of action of the primary drug interaction, a statement discussing this involvement appears in the related drug section of the monograph.

   If more than three agents exist in that particular class, only three representative agents are listed in parenthesis followed by [see Appendix]. The user may refer to the Appendix of Related Drugs, which will contain a complete list of other agents in a related drug class.

   Agents that are no longer commercially available in the United States have not been included in this edition unless it was necessary to discuss a noteworthy drug interaction, in which case it is noted by an asterisk that the agent is not commercially available in the United States. An agent that is currently in research or one that is soon to be marketed has been included within the monograph if medical literature and documentation are available.
4. *Mechanism.* This is a discussion of the proposed or postulated mechanism for the drug interaction.
5. *Recommendations.* Suggested management to be considered by the practitioner in regard to the specific drug interaction is given here.
6. *References.* These have been footnoted numerically in order of appearance within the monograph. Other reference sources that have been reviewed but not specifically cited within the monograph are not included.

User's Guide

CHAPTER ASSIGNMENTS

In an attempt to uniformly classify the drug-to-drug interaction monographs by their categories, eighteen chapters have been devised. Each monograph is assigned a chapter depending upon classification and pharmacologic effect. Criteria used for this assignment are:

1. The first drug listed in the monograph heading designates its alphabetical chapter assignment. This will be the drug whose pharmacologic effect is altered by the second drug in the combination. However, if the affected drug does not have a chapter cited (other than the miscellaneous chapter), the above does not apply. Instead, the monograph is placed alphabetically in the therapeutic chapter of the other agent.
2. For the drug interactions where neither of the two involved agents has an assigned chapter, the monographs are listed in the Miscellaneous Drug Interaction chapter (Chapter 18) and are listed in alphabetical order by the drug whose pharmacologic action is altered.

It is intended by the editors that this classification will enable the user to more efficiently identify those agents that may alter the desired effects of the patient's prescribed regimen.

SIGNIFICANCE CODING

Each drug-drug interaction has been assigned a significance code based on three major factors: (1) potential harm to the patient, (2) frequency and predictability of occurrence, and (3) degree and quality of documentation.

The editors, consulting contributors, and the interdisciplinary review panel have applied these factors to each drug interaction and assigned a significance code to each monograph heading. The significance code is to be considered applicable only to the agents that appear in the header of the monograph. The related drugs that are mentioned or discussed in the monograph are not given a significance code.

Code 1. *Highly clinically significant:* includes drug interactions that are of great potential harm to the patient, are predictable or occur frequently, and are well documented.

Code 2. *Moderately clinically significant:* drug interactions that are of moderate potential harm to the patient, are less predictable or occur less frequently, or lack complete documentation.

Code 3. *Minimally clinically significant:* drug interactions that are of little potential harm to the patient, have variable predictability or occur infrequently, or have little documentation.

Code 4. *Not clinically significant:* although these drug interactions may occur, documentation may be based on theoretical considerations or the resulting effects of the interactions are not clinically significant and no adverse effects would be anticipated to occur.

NOTICE

This publication does not purport to include all reported drug interactions. All expressions of opinion and statements presented in this publication concerning the incidents and severity of possible drug interactions—as well as recognition, side effects, and treatment of such interactions—represent the consensus of the staff and consultants of Professional Drug Systems, Inc., and the American Pharmaceutical Association Scientific Review Panel, acting under the direction of the staff of the American Pharmaceutical Association.

This book is intended for professional use by health professionals and should not be used by anyone who does not have such specialized training. This book can serve to assist the practitioner, but it is not a substitute for professional knowledge, judgment, training, and experience.

The developers of this work have attempted in the monographs to reflect the true meaning of the articles being reviewed. However, how each monograph relates to other drugs in its therapeutic class or other dosage forms of the drug not specifically referred to by the monograph requires professional interpretation by the user on a case by case basis. In addition, in view of the ongoing research and development relating to new agents, drugs, drug therapy, and drug interactions and reactions, the practitioner is cautioned to consult carefully the package inserts for drugs prior to their administration for added precautions and warnings.

The inclusion in this publication of the drug in respect to which patent or trademark rights may exist shall not be deemed, and is not intended as, a grant of, or authority to exercise, any right or privilege protected by such patent or trademark. All such rights and privileges are vested in the patent or trademark owner, and no other person may exercise the same without express permission, authority, or license secured from such patent or trademark owner.

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