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YEAR BOOK OF DRUG THERAPY® 1990

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1990

The Year Book of DRUG THERAPY®

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Journals Represented

Year Book Medical Publishers subscribes to and surveys nearly 850 U.S. and foreign medical and allied health journals. From these journals, the Editors select the articles to be abstracted. Journals represented in this YEAR BOOK are listed below.

Acta Cardiologica
Allergy
American Family Physician
American Heart Journal
American Journal of Cardiology
American Journal of Clinical Pathology
American Journal of Diseases of Children
American Journal of Medicine
American Journal of Obstetrics and Gynecology
American Journal of Ophthalmology
American Journal of Pediatric Hematology/Oncology
American Journal of Psychiatry
American Journal of Surgery
American Journal of the Medical Sciences
American Review of Respiratory Disease
Anesthesia and Analgesia
Anesthesia Progress
Annals of Allergy
Annals of Emergency Medicine
Annals of Internal Medicine
Annals of Rheumatic Diseases
Annals of Surgery
Annals of the Royal College of Surgeons of England
Anticancer Research
Archives of Dermatology
Archives of Disease in Childhood
Archives of General Psychiatry
Archives of Internal Medicine
Archives of Ophthalmology
Archives of Otolaryngology–Head and Neck Surgery
Archives of Physical Medicine and Rehabilitation
Archives of Surgery
Arthritis and Rheumatism
Atherosclerosis
Biological Psychiatry
British Journal of Cancer
British Journal of Clinical Pharmacology
British Journal of Dermatology
British Journal of Psychiatry
British Journal of Surgery
British Medical Journal
Canadian Journal of Neurological Sciences
Canadian Journal of Psychiatry
Cancer
Chest
Circulation
Clinical Chemistry

Clinical Nephrology
Clinical Pharmacology and Therapeutics
Clinical Radiology
Comprehensive Psychiatry
Contraception
Critical Care Medicine
Cutis
Diabetic Medicine
Digestive Diseases and Sciences
Drug and Alcohol Dependence
Epilepsia
European Journal of Clinical Pharmacology
European Journal of Haematology
European Journal of Pharmacology
European Journal of Vascular Sugery
European Respiratory Journal
Fertility and Sterility
Gastroenterology
Headache
Hepatology
Hypertension
International Journal of Cardiology
Israel Journal of Medical Sciences
Journal of Allergy and Clinical Immunology
Journal of Bone and Joint Surgery (American volume)
Journal of Cardiovascular Pharmacology
Journal of Clinical Endocrinology and Metabolism
Journal of Clinical Epidemiology
Journal of Clinical Investigation
Journal of Clinical Oncology
Journal of Clinical Pharmacology
Journal of Clinical Psychiatry
Journal of Clinical Psychopharmacology
Journal of Consulting and Clinical Psychology
Journal of Emergency Medicine
Journal of Hand Surgery (American)
Journal of Hypertension
Journal of Infectious Diseases
Journal of Laboratory and Clinical Medicine
Journal of Neurology, Neurosurgery and Psychiatry
Journal of Oral and Maxillofacial Surgery
Journal of Pediatric Gastroenterology and Nutrition
Journal of Pediatrics
Journal of Pharmacology and Experimental Therapeutics
Journal of Rheumatology
Journal of Surgical Research
Journal of Thoracic and Cardiovascular Surgery
Journal of Urology
Journal of the American Academy of Child and Adolescent Psychiatry
Journal of the American Academy of Dermatology
Journal of the American College of Cardiology
Journal of the American Geriatrics Society

Journal of the American Medical Association
Journal of the Canadian Association of Radiologists
Journal of the National Cancer Institute
Journal of the Royal College of Surgeons of Edinburgh
Kidney International
Klinische Wochenschrift
Lancet
Life Sciences
Mayo Clinic Proceedings
Medical Care
Mount Sinai Journal of Medicine (New York)
Nephron
Neurology
New England Journal of Medicine
Obstetrics and Gynecology
Ophthalmology
Oral Surgery, Oral Medicine, Oral Pathology
Pain
Pediatric Infectious Disease Journal
Pediatrics
Pharmacotherapy
Physician and Sports Medicine
Postgraduate Medical Journal
Respiration
S.A.M.J./S.A.M.T.—South African Medical Journal
Scandinavian Journal of Gastroenterology
Scandinavian Journal of Primary Health Care
Scandinavian Journal of Rheumatology
Seminars in Oncology
Southern Medical Journal
Stroke
Thorax
Transplantation
VASA: Zietschrift fur Grefasskrankheiten
Western Journal of Medicine

Publisher's Preface

Publication of the 1990 YEAR BOOK OF DRUG THERAPY marks the end of an outstanding era of YEAR BOOK Editorship by Leo E. Hollister, M.D. During Dr. Hollister's 14 years of editorship, the volume's readers have been treated to literature selections and editorial commentary of the highest caliber. We extend our deepest appreciation for the service Dr. Hollister has provided and for his ever-present support and enthusiasm for the YEAR BOOK.

Beginning with the 1991 YEAR BOOK OF DRUG THERAPY, Michael Weintraub, M.D., will be joining Louis Lasagna, M.D., as the volume's co-Editor. Dr. Weintraub is Associate Professor of Preventive Medicine, Pharmacology, and Medicine at the University of Rochester School of Medicine. We welcome him while we thank Dr. Lasagna for his continuing commitment for his many years of excellent contribution.

Introduction

As in past years, the 1990 YEAR BOOK OF DRUG THERAPY represents the editor's choice of some 350 articles, chosen from a long list of journals as those most likely to be of interest to our readers. In general, we have avoided articles that, although scientifically interesting, are difficult to relate—at least for the moment—to the practice of medicine.

The pace of research continues to be mind-boggling, but new facts unearthed in the laboratory may wait a long time (and perhaps forever) before they are integrated into a clinical nexus that will pay either diagnostic or therapeutic dividends. This lag is well exemplified by the time that traditionally elapses between the research that ultimately wins a Nobel Prize in Medicine and the actual awarding of the prize.

The other side of the coin has to do with the opposite type of development: the gradual or sudden decline in the attention paid to an old scientific finding as time fails to replicate the data of the original researcher. For both discovery and rejection, keeping up with the literature is essential. We hope that the YEAR BOOK helps our readers in both respects.

This edition represents the swan song of one of the editors. Leo Hollister has performed ably and selflessly in his capacity as Editor, and those of us who will carry on with future editions wish Leo well. We miss him already!

Louis Lasagna, M.D.

Table of Contents

The material in this volume represents literature reviewed through June of 1989.

1 General Information

Survey Method for Post-Marketing Drug Surveillance: A Demonstration

Mellinger GD, Balter MB, Abramowitz S, Schaffer CB, Bernstein LR (Inst for Research in Social Behavior, Oakland, Calif; Natl Inst of Mental Health, Rockville, Md; Univ of California, Davis; Univ of California, San Francisco)

J Clin Psychopharmacol 8:168–176, June 1988 1–1

Postmarketing drug surveillance (PMDS) offers the opportunity to study efficacy and safety under conditions that were absent or excluded in the initial clinical trials. The results from a demonstration project in which a community survey method was applied to a PMDS were evaluated.

Representative samples of outpatients treated with tricyclic antidepressants or benzodiazepine anxiolytics were identified and interviewed at baseline and at specified intervals at home or by phone. Lay interviewers trained to use a detailed interview schedule collected the data. The degree to which predicted outcomes for the 2 well-studied drug classes matched observed outcomes was determined. Two contrast groups, 3 measurement periods, and 6 key symptoms measures were involved. The results were consistent with expectations.

This method of PMDS proved to be highly discriminating and sensitive. It could detect less common events with samples that are larger but still feasible, especially if data were collected over a long time and the outcomes were patterned.

➤ We need to pay much more attention than has been paid in the past to the benefits and harm from drugs as used in actual practice, which is not at all the same as a controlled trial. Mellinger, Balter, and their colleagues have pioneered in imaginative surveys of patient attitudes and drug taking. This paper is well worth reading in its original form to appreciate the subleties and potential importance of the described technique.—L. Lasagna, M.D.

Indigenised Pharmaceuticals in Developing Countries: Widely Used, Widely Neglected

Haak H, Hardon AP (Univ of Amsterdam)

Lancet 2:620–621, Sept 10, 1988 1–2

In the Philippines and Brazil, many modern pharmaceuticals are now widely used and sold without a prescription, indicating that these products are used for self-medication. Research indicates that in both countries western pharmaceuticals are increasingly becoming "indigenized," i.e., incorporated into the local culture. Most of these products have long been commercially available, and patients have become familiar with them partly through physicians' prescriptions and partly through self-medication by trial and error. Indigenized products

are widely available in cafes and shops at low costs and are now rarely prescribed by physicians.

In the Philippines, Diatabs, which contain sulfaguanadine, charcoal, bismuth subcarbonate, pectin, and dicyclomine HCl, have become indigenized, as have Polymagma and penicillin tablets. In Brazil, oxytetracycline and tetracycline HCl are considered indigenized pharmaceuticals. Modern pharmaceuticals are now even prescribed by traditional healers for the most trivial indications.

Health workers and planners of health programs are advised to familiarize themselves with the self-medication practices of prescription-only drugs in these countries.

➤ It is fascinating to see how western drugs have invaded the developing countries, with resultant use not only by the public without medical intermediaries but by native system practitioners like Ayurvedic practitioners! The question that no one can answer is: Has this done more good than harm, or vice versa?—L. Lasagna, M.D.

The Effects of an Internal Analgesic Formulary Restriction on Medicaid Drug Expenditures in Wisconsin

Kreling DH, Knocke DJ, Hammel RW (Univ of Wisconsin–Madison)

Med Care 27:34–44, January 1989 1–3

In an effort to contain the costs of prescription drugs, the Wisconsin Medicaid prescription drug program uses a Negative Drug List. On February 1, 1985, products containing propoxyphene napsylate were removed from the Wisconsin Medicaid drug program and added to the Negative Drug List. Thus these products were no longer eligible for reimbursement. The internal analgesic expenditures and usage data were studied for the 3-month periods before and after removal of propoxyphene napsylate products.

After adjusting for price and reimbursement changes between the 2 study periods, the overall expenditures after removal of propoxyphene napsylate products from the formulary were actually slightly higher. Propoxyphene hydrochloride was the most widely prescribed substitution drug for institutional patients. A smaller proportion of propoxyphene napsylate prescriptions was converted to propoxyphene HCl for the noninstitutional patients, as they seemed to have been switched over more often to nonsteroidal anti-inflammatory products, which are more expensive but probably more effective. Although no cost savings were achieved by removing propoxyphene napsylate from the Wisconsin Medicaid drug program formulary, the removal may have had a therapeutic advantage for the patients.

➤ An important study. There is no doubt that taking drugs out of formulary reimbursement status decreases their use. But doctors and patients will then substitute something else: in this case, NSAIDs (nonsteroidal anti-inflammatory drugs) were most often used in place of propoxyphene napsylate. The object was to save money; the decision did not achieve this goal. (In fact, overall analgesic expenditures went up slightly, after adjustment for temporal price and reimbursement policy changes.) One can only speculate as to whether the patients were better off on NSAIDs.—L. Lasagna, M.D.

Antibiotic Cost Reduction by Providing Cost Information

Rubinstein E, Barzilai A, Segev S, Samra Y, Modan M, Dickerman O, Haklai C (Tel-Aviv Univ)

Eur J Clin Pharmacol 35:269–272, 1988 1–4

Approximately 30% of all hospitalized patients are treated with antibiotics; however, approximately two thirds of total antibiotic therapy is not indicated or is inappropriately prescribed. In an attempt to reduce hospital expenditure on antibiotics, the effect of adding antibiotic cost information to the computerized printout of a patient's microbiology culture results was evaluated. The cost of each antibiotic was listed next to the sensitivity data. The study was done in a general hospital in Israel.

During the first 6 months of the study the average monthly expenditures for antibiotics decreased by 16.5%, or $7,636, when compared with the preceding 12-month period. The decrease in the use of aminoglycosides alone accounted for an average monthly savings of $2,733 (Fig 1–1). The average reduction in the cost of antibiotics per admission was $1.61 (15.7%). Of the average monthly amount saved, $2,850 (37.3%) came from antibiotics on the restricted list, the use of which required authorization by an infectious disease consultant. The rest was saved by the house staff. The impact of this system on treatment outcomes remains to be evaluated.

➤ New antibiotics keep being developed and are welcome additions to the ever challenging fight against infectious disease. Unfortunately, most of the newer entries are very expensive, even though well worth the price when they are really needed.

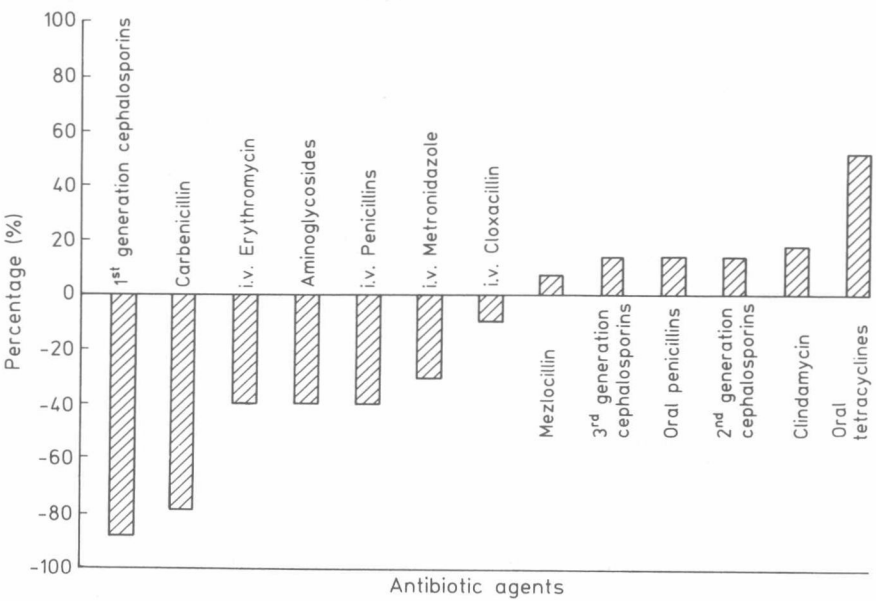

Fig 1-1.—Average change in monthly antibiotic expenditure after introduction of the price information system. (Courtesy of Rubinstein E, Barzilai A, Segev S, et al: *Eur J Clin Pharmacol* 35:269–272, 1988.)

Many physicians prescribe the newer and more expensive antibiotics for situations that can be managed equally well with older, cheaper drugs. Letting the physician know the cost of drugs may help reduce overall expenditures. Some years ago, I suggested facetiously that we pay our residents $80,000 a year but make them pay for the drugs they prescribe. When money does not come from one's own pocket, there is little incentive to save.—L.E. Hollister, M.D.

Additives Contained in Drug Formulations Most Frequently Prescribed in Switzerland

Kolly M, Pécoud A, Frei PC (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland)

Ann Allergy 62:21–25, January 1989 1–5

The production of pharmaceuticals commonly involves the use of such additives as dyes, preservatives, antioxidants, emulsifiers, stabilizing agents, thickeners, sweeteners, or flavors. Any of these additives may induce idiosyncratic or pseudoallergic reactions in susceptible individuals, even though hypersensitivity reactions have been well documented only for parabens and sulfites. The actual number and types of chemicals added to drug products is not well known. Data were collected on all chemicals added to 1,467 formulations of 915 compounds commonly prescribed in Switzerland by mailing a questionnaire to the pharmaceutical manufacturers of these products.

Of the 1,467 formulations, 60% were solid oral forms, 17% were liquid oral forms, 13% were injectables, 4% were suppositories, and 2% were solutions for inhalation. All products were surveyed for the presence of 5 major preservatives and 7 major dyes (table).

Proportion of the 1,467 Formulations Studied Containing One or the Other of 5 Preservatives and 7 Coloring Agents

Additive	No of Formulations	% of All Formulations Studied
Benzoates	226	15.4
Sorbates	80	5.5
Sulfites	56	3.8
Benzalkonium	44	3.0
BHA and BHT	10	0.7
None of those 5 preservatives	1,113	76.0
Indigotin	114	7.8
Erythrosine	109	7.4
Sunset yellow	97	6.6
Tartrazine	72	4.9
Quinoleine yellow	41	2.8
Ponceau 4R	38	2.6
Amaranth	25	1.7
None of those 7 dyes	1095	75.0
None of those 12 additives	827	57.0

(Courtesy of Kolly M, Pécoud A, Frei PC: *Ann Allergy* 62:21–25, January 1989.)

Although for susceptible patients the risk of exposure to additives used in drugs is smaller than that when taking food, the possibility of a sensitivity to additives should be considered in all cases of adverse drug reactions when the role of the active compound is questionable.

➤ Food and drug additives are not trivial causes of untoward reactions. Sulfites, tartrazine, benzoates, and parabens, e.g., have all been repeatedly incriminated as causes of adverse effects. Differences in manufacture between different versions of the same drug with reference to presence or absence of certain additives may pose trouble for patients even when the bioavailability is the same. The FDA assures consumers that the possibility is not ignored, but how can you detect allergic reactions by studying a few dozen healthy male volunteers?—L. Lasagna, M.D.

Worldwide Variation in Chloramphenicol Utilization: Should It Cause Concern?
Kumana CR, Li KY, Chau PY (Univ of Hong Kong; Queen Mary Hosp; Med and Health Dept, Hong Kong)
J Clin Pharmacol 28:1071–1075, 1988 1–6

Chloramphenicol therapy has been restricted to a limited number of indications because it can lead to aplastic anemia. However, in Hong Kong large amounts of chloramphenicol are used as antimicrobials for both children and adults. Therefore the extent to which chloramphenicol contributes to the local incidence of aplastic anemia was studied.

Per capita sales of chloramphenicol in Hong Kong were 22–442 times greater than in several western countries and Australia (table). Despite such exposure the certified death rate from aplastic anemia (regardless of identifiable cause) in Hong Kong was only 0.4/1,000 deaths, compared with 1.0/1,000 deaths in England and Wales. No other evidence was found to indicate that Hong Kong residents experienced an excessive incidence of aplastic anemia.

Although the amounts of chloramphenicol sold in Hong Kong are high, the extent to which such widespread consumption contributes to aplastic anemia appears to be lower than expected. Because of the alleged high risk of chloramphenicol-induced aplastic anemia, there is urgent need for prospective investigations in local populations to reevaluate these risks.

➤ When a country reports little trouble from chloramphenicol, the temptation is to blame it on poor hospital records. This is not an attractive notion in the case of Hong Kong. Because the antibiotic is cheap, free of most side effects, and effective against many microorganisms, its use should not be dismissed without good reason. I don't know what these authors mean, however, by the term *prospective investigations* in this instance. The occurrence of aplastic anemia after chloramphenicol in the United States, for example, is generally conceded to be no greater than 1 in 20,000, not the kind of incidence that yields readily to prospective studies.—L. Lasagna, M.D.