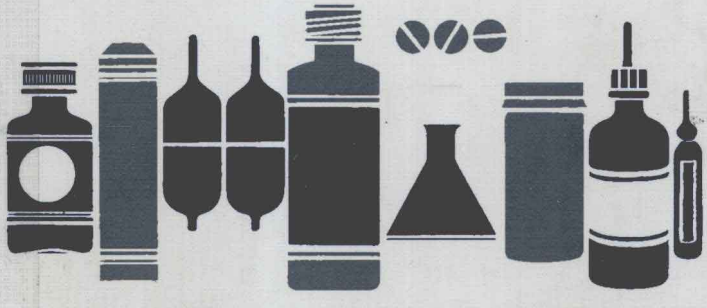
SIDE EFFECTS OF DRUGS ANNUAL 32

J.K. ARONSON



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SIDE EFFECTS OF DRUGS ANNUAL 32

A worldwide yearly survey of new data and trends in adverse drug reactions and interactions

EDITOR

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How to use this book

THE SCOPE OF THE ANNUAL

Volumes in the *Side Effects of Drugs Annual* (SEDA) series have been published since 1977. The series is designed to provide a critical account of new information relating to adverse drug reactions and interactions from the clinician's point of view. It complements the standard encyclopedic work in this field, *Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions*, the 15th edition of which was published in 2006.

PERIOD COVERED

The present *Annual* reviews all reports that presented significant new information on adverse reactions to drugs during 2007 and the first half of 2008; the next volume (SEDA-33) will cover the second half of 2008 and all of 2009. During the production of this *Annual*, some more recent papers have also been included; older literature has also been cited when it is relevant. Special reviews (see below) often cover a much wider range of literature.

SELECTION OF MATERIAL

In compiling the *Side Effects of Drugs Annual* particular attention is devoted to publications that provide essentially new information or throw a new light on problems already recognized. Some confirmatory reports are also described. In addition, some authoritative new reviews are listed. Publications that do not meet these criteria are omitted. Readers anxious to trace all references on a particular topic, including those that duplicate earlier work, or to cross-check an electronic search, are advised to consult *Adverse Reactions Titles*, a monthly bibliography of titles from about 3400 biomedical journals published throughout the world, compiled by the Excerpta Medica International Abstracting Service.

Special reviews

The special reviews deal in more detail with selected topics, often interpreting conflicting evidence, providing the reader with clear guidance. They are identified by the traditional prescription symbol and are printed in italics. This volume includes a Cumulative Index of the Special Reviews that were published in SEDA-11 to SEDA-31 and a list of the Special Reviews that appear in the current Annual.

CLASSIFICATION OF DRUGS

Drugs are classified according to their main field of use or the properties for which they are most generally recognized. In some cases a drug is included in more than one chapter (e.g. lidocaine is mentioned in Chapter 11 as a local anesthetic and in Chapter 17 as an antidysrhythmic drug). Fixed combinations of drugs are dealt with according to their most characteristic component or as a combination product.

DRUG NAMES

Drugs are usually called by their recommended or proposed International Non-proprietary Names (rINN or pINN); when these are not available, chemical names have been used. If a fixed combination has a generic combination name (e.g. co-trimoxazole for trimethoprim + sulfamethoxazole) then that name has been used; in some cases brand names have been used instead.

SYSTEM OF TAGGING REFERENCES

References in the text are tagged using the following system, which was introduced in SEDA-24:

M A meta-analysis or other form of systematic review;
A An anecdote or set of anecdotes (i.e. case histories);
R A major review, including non-systematic statistical analyses of published studies;
r A brief commentary (e.g. an editorial or a letter);
C A major randomized controlled trial or observational study;
c A minor randomized controlled trial or observational study or a non-randomized study;
H A hypothesis article;
E An experimental study (animal or in vitro);
S Official (e.g. Governmental, WHO) statements.

The various editions of *Meyler's Side Effects of Drugs* are cited in the text as SED-l4, SED-15, etc.; the *Side Effects of Drugs Annuals 1–31* are cited as SEDA-1, SEDA-2, etc.

INDEXES

Index of drugs: this index provides a complete listing of all references to a drug for which adverse effects and/or drug interactions are described.

Index of adverse effects: this index is necessarily selective, since a particular adverse effect may be caused by very large numbers of compounds; the index is therefore mainly directed to adverse effects that are particularly serious or frequent, or are discussed in special detail; before assuming that a given drug does not have a particular adverse effect, consult the relevant chapters.

For indexing purposes American spelling has been used, for example anemia, estrogen rather than anaemia, oestrogen.

Kelvin Chan[1]

SIDE EFFECTS OF DRUGS ESSAY

Regulating complementary and alternative medicines

Over the past decade, the increasing popularity of complementary and alternative medicines (CAM) and over-the-counter (OTC) health foods and supplements, nutraceuticals and medicinal products from plants or other natural sources (inclusively known as botanicals, including herbal medicines, or phytomedicines) has also brought concerns about the professionalism of practitioners, and about the quality, efficacy, and safety of their treatment methods and the available products that are derived from herbal and natural sources (1^R).

These OTC products may contain excessive or banned pesticides, microbial contaminants, chemical toxins and other contaminants or adulterants, such as heavy metals, and pharmaceuticals. Contaminants can come from locations where the plants are grown, collected, or processed. Toxins can come from poor storage conditions. The presence of pharmaceuticals may be illogically claimed to be due to accidental contamination during production; however, such products are also manufactured unprofessionally and are deliberately adulterated (2^R).

Environment-related factors can be controlled by implementing standard operating procedures (SOP), leading to Good Agricultural and Collection Practice (GACP), Good Laboratory Practice (GLP), Good Supply Practice (GSP), and Good Manufacturing Practice (GMP) for producing these medicinal products, before Good Clinical Trial Practice (GCTP) for evaluation of efficacy. Therefore, regulatory policies should be set up to oversee the quality and safety of these products before they are made available to the public as OTC medicines, or for prescription. The public's faith in herbal and natural products, which they believe (often incorrectly) to be safer than synthetic pharmaceutical medicines, can only be rewarded by instituting regulatory controls on these products, which demand that they should provide traceability of their sources and manufacture, using good codes of practice. Some national government authorities have set up regulatory controls over the starting materials that are supplied to herbal companies for the manufacture of herbal products in order to safeguard the interests of the public.

In this essay I focus on the progress of regulatory standards (3^S–5^S). Some academic and professional bodies have also taken initiatives to build reliable and reputable databases for monitoring the adverse

[1]The author of this year's Side Effects of Drugs Essay is Kelvin Chan PhD, DSc, FSB, FCP, FRPharmS, FRSM. Professor Chan is Joint Chair Professor in Traditional Chinese Medicine at Faculty of Pharmacy, University of Sydney, NSW2006, and at the College of Health and Science, University of Western Sydney, NSW2560, Australia.

effects of CAM, and we shall summarize the key reviews that have been published (6^R, 7^R).

Australia and New Zealand (3^S)

In Australia and New Zealand complementary medicines, including herbal, minerals, nutritional/dietary supplements, aromatherapy oils and homeopathic medicines, are regulated under therapeutic goods/products legislation. The Therapeutic Goods Administration (TGA), a division of the Commonwealth Department of Health and Ageing, is responsible for administering the provisions of the legislation in Australia. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) administers the provision of legislation in New Zealand. In December 2003 the Australian and New Zealand governments signed a treaty to establish a single, binational agency to regulate therapeutic products, including medical devices prescription, OTC medicines and complementary medicines.

The single agency has replaced Medsafe in New Zealand and the TGA in Australia. The role of this agency is to safeguard public health through regulation of the quality, safety and efficacy or performance of therapeutic products in both countries. The major activities of the new joint Australia New Zealand Therapeutic Products Agency are in product licensing, specifying labelling standards and setting advertising schemes, as well as determining the risk classes of medicines and creating an expanded list of ingredients permitted in Class I medicines.

A new, expanded definition of complementary medicines has been proposed, and this definition is currently under consultation. Related Australian and New Zealand legislation is being developed to implement the joint scheme. Once this legislation is passed, the Treaty will come into force and the new joint regulatory scheme will begin. The agency was originally expected to commence operation no later than 1 July 2006 and to result in a single agency to regulate CAM. However, consultation continues. In Australia, there has been an initiative to introduce nationwide registration of traditional Chinese medicine (TCM) practitioners by 2012.

China (4^S)

China's National Center for Adverse Drug Reaction (ADR) Monitoring was established in 1989, before China joined the World Health Organization's Programme for International Drug Monitoring in 1998. In March 2004, China formally promulgated the final version of the Regulations on Adverse Drug Reaction Reporting and Monitoring. This modern system supplements an informal reporting system in scholarly publications.

Procedurally, the formal Chinese monitoring system requires pharmaceutical companies and health-care professionals to report most adverse events quarterly. However, new, uncommon, serious or 'group' adverse events are required to be reported within a shorter period. Reports are made to local centres, which then analyse and transmit them to a national ADR centre operated by China's State Food and Drug Administration (SFDA). The national authority is then empowered to authorize further studies, publish formal warning announcements or prohibit the use of a product.

TCM products are also regulated as drugs in China. Because the use of TCM products is increasing worldwide, Chinese adverse reactions monitoring is particularly, if not uniquely, useful in reporting

of TCM-related adverse drug reactions. A survey of Chinese ADR alerts and findings regarding TCMs and other substances is included, providing an overview of the breadth and timeliness of the information available from China's increasing pharmacovigilance activity. Overall, the system shows considerable progress and promise, especially if awareness of the procedures for reporting suspected ADRs continues to grow among China's healthcare professionals and public.

Hong Kong Chinese Materia Medica Standards (HKCMMS) (5^S)

The Department of Health (DOH) in Hong Kong's SAR Government initiated the HKCMMS project in 2003 and commissioned experts available in the local universities and research institutes to take part in experimental and research work in setting standard guidelines and monographic standards for the quality and safety of Chinese medicinal materials (CMM) available in Hong Kong and Mainland China.

The standard criteria include chromatographic fingerprints and assay values of markers of Chinese medicinal materials, together with all the required monographic data in established pharmacopoeias, such as the British, Chinese, European, Japanese, and US Pharmacopeias.

Generation of these data is overseen and advised by an International Advisory Board of renowned experts from various countries and regions in Australia, Canada, China, Germany, Japan, Thailand, the UK, and the USA.

A recent 'Commentary article' has given an overview of the encouragement of a global agreement on harmonizing pharmacopeia monographic standards of

Table 1. *Pharmacopoeia or standards of various countries or regions that have monographic standards for Chinese medicinal materials (modified from reference 6)*

Pharmacopoeia or monograph	**Authority**	**Status and remarks**
WHO Monographs on Selected Medicinal Plants	World Health Organization, Geneva	Four volumes; unofficial
Pharmacopoeia of the People's Republic of China (CP)	State Food and Drug Administration (SFDA), PR China	Official
Australian Regulatory Guidelines for Complementary Medicines	Therapeutic Goods Administration (TGA), Australia	TGA, Official
European Pharmacopoeia	European Directorate for the Quality Medicines & Healthcare (EDQM)	Official
Hong Kong Chinese Materia Medica Standards	Department of Health, Hong Kong SAR, PR China	Official
Japan Pharmacopoeia	The Pharmaceutical Affairs	Official
Thai Herbal Pharmacopoeia	Thai Food and Drug Administration, Ministry of Public Health	Official
British Pharmacopoeia	British Pharmacopoeia Commission, MHRA, UK	Official
American Herbal Pharmacopeia (AHP); contains some monographs on Chinese medicinal materials	Dietary Supplements Health and Education Act (DSHEA) decides that botanicals are treated as food supplements	Unofficial
Chinese Drug Monographs and Analysis	Kotzting/Bayer. Wald, Germany	Verlag für Ganzheitliche Medizin – Dr Erich Wuhr GmbH; unofficial

Chinese medicinal materials, such that the quality of these starting herbal ingredients can be assured for the practice of TCM and the manufacture of Chinese medicinal products (6^R).

Table 1 summarizes the major standards in various countries and regions for reference.

Initiative on International Standards for Data Collection (7^R)

Research on morbidity from TCM is an emerging field. Currently, not much is known and there is a lack of international standards for data collection and reporting.

Based on the experience of developing a computerized system for patient data collection by colleagues at the University of Technology Sydney (UTS) Acupuncture Clinic and reporting results from that database, a start can be made towards developing guidelines for reporting similar results from TCM clinical audits.

This study has reported data relating to 5735 patients who had undergone 29 697 courses of treatment. Patient information is collected by a computerized database recording the International Classification of Primary Care (ICPC), reason for encounter (RFE) and symptom for encounter (SFE) data, and TCM tongue, pulse, diagnostic, and treatment data. Data coding is automated, and systems for reliability testing and error reporting have been developed. The UTS database has a 2.7% error rate and is within international standards of 5% error.

Musculoskeletal disorders are the most common presentation (41%) of all RFE, followed by general disorders (13%) and digestive disorders (8.1%).

International standards must be set for TCM morbidity data collection methods and reporting. It is hoped that the methods described and reported in this paper are an initial step in the setting of such standards and that they will be adopted by other researchers. In particular, methods for testing and reporting data reliability must be adopted if TCM morbidity studies are to maintain any credibility.

Conclusion

Differences among national or regional regulations on the import and export of medicinal plants can affect the quality control of herbal products. The same medicinal plant products may be classified as foods, food supplements, functional foods, nutriceuticals, or prescribed herbal medicines in different countries or regions. A harmonized regulatory system in pharmacopeial standards of herbal materials generated from medicinal plants would improve the quality of herbal materials, thereby ensuring the safety of manufactured herbal products and assisting herbal practitioners.

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