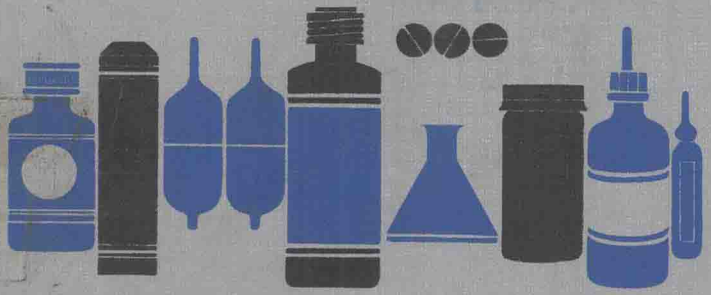
M.N.G. DUKES

SIDE EFFECTS OF DRUGS ANNUAL 3 1979



EXCERPTA MEDICA

SIDE EFFECTS OF DRUGS ANNUAL 3

A worldwide yearly survey of new data and trends

EDITED BY

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Vice-Chairman, Netherlands Committee for the Evaluation of Medicines

1979

EXCERPTA MEDICA, Amsterdam - Oxford

ISBN Excerpta Medica 90 219 3045 5

ISBN Elsevier/North-Holland 0 444 90072 1

Library of Congress Catalog Card Number A59-1584

Publisher:
Excerpta Medica
305 Keizersgracht
1000 BC Amsterdam
P.O. Box 1126

Sole distributors for the USA and Canada:
Elsevier/North-Holland Inc.
52 Vanderbilt Avenue
New York, N.Y. 10017

Typeset and printed by Dijkstra Niemeyer bv, Groningen

Complementary to this volume:

MEYLER'S SIDE EFFECTS OF DRUGS, VOLUME VIII, 1975
An encyclopaedic survey of unwanted effects of drugs as reported up to 1975
Edited by M. N. G. Dukes
xvi + 1132 pages, over 10,000 literature references
ISBN 90 219 9160 8

SIDE EFFECTS OF DRUGS ANNUAL 1 – 1977
Edited by M. N. G. Dukes
xvii + 420 pages
ISBN 90 219 3038 2

SIDE EFFECTS OF DRUGS ANNUAL 2 – 1978
Edited by M. N. G. Dukes
xix + 450 pages
ISBN 0 444 90023 3

wanted and unwanted drug effects: the need for perspective

Louis Lasagna

The last two decades have seen an ever increasing preoccupation on the part of both society as a whole and the medical profession in particular with the adverse effects of chemicals, including medicines. The reasons are well known, and include both real instances of harm to humans from therapeutic substances, illicit drugs, pesticides, occupational exposure, and the effluvia of chemical plants on the one hand, and the fears raised by experiments in animals (or even bacteria!) with chemicals given in astronomical doses, on the other hand.

It is not surprising that such events have attracted the attention of the news media, environmentalists, consumer advocates and the elected representatives of the people. What *is* surprising is how little scientists have done to educate the public to the fact that all of life is a cost-benefit calculus, and that we forget this unassailable fact at our peril.

How does this pertain to unwanted drug effects? It means that whenever society considers the use of chemicals, its decisions will in general be deleteriously affected by faulty data about either the expected benefits or the putative harms from such use. Those who oppose digging for oil in the North Sea or off the coast of the United States because such digging may adversely affect the ocean's oecology on the adjacent beaches must consider the risks of *not* digging for oil. Those who object to the possible hazards of food preservatives must weigh the harm that accrues to a population from food wastage or deterioration.

Similarly, those who wish to ban medicines because some people abuse them, or incur serious harm from their use, should first construct the social calculus that would obtain if such drugs were not available to anyone.

Some will say that we do this already. That statement is partly true. Only a fool prescribes powerful anti-cancer drugs without cognizance of their fearsome potential for toxicity. But for some cancer patients, at least, the benefits can outweigh the risk. The general assertion that 'we do this already' ignores our pitifully imprecise knowledge about most drugs as well as disagreements in the area of value judgements. By 'pitifully imprecise' I refer to the lack of quantification about both the good and bad effects of any drug or of the available alternatives to a drug when such alternatives exist.

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* The Side Effects of Drugs Essay is written each year by guest authors from the various countries which contribute to the Annual. Dr. Lasagna is Professor of Pharmacology and Toxicology at the University of Rochester, NY.

Consider, for example, what a well-programmed computer would need in order to give good advice about the management of a hypertensive patient. What are the relative merits of salt restriction alone, e.g., versus drugs? Of the available drugs, how do they perform, *vis à vis* one another, when used optimally? Are some easier to use than others? Is compliance better with some than others? Is the therapeutic ratio better for some than for others? Are the long-term effects (good *and* bad) more attractive for some drugs? How does organ insufficiency (heart, kidney, brain, e.g.) affect one's choice? Or age? What level of high blood pressure is worth treating? At what level of blood pressure reduction should we aim? The list of questions does not end with the ones posed above, but they at least make my point, I hope.

It is foolish to ignore the value judgement aspect of the answers to some of these questions. How much in the way of side effects will be tolerated by a physician treating himself for hypertension may well differ from what will be tolerated by some or all of his patients. Sedation may bother some people more than does impotence, and vice versa for others. Some patients will tolerate little in the way of *any* side effects, since hypertension is so often asymptomatic *until* drug treatment is undertaken.

The value judgement aspect is even trickier in situations where the desirability of *any* drug treatment is contested fiercely. Many look with scorn, for example, on the use of minor tranquillizers or appetite suppressants. Such critics of their use either consider 'the anxieties of everyday life' or the existence of overweight to be evidence of a simple lack of moral fibre on the part of the sufferers, or at the very least question the efficacy, safety, or both, of the drugs used in the management of these 'ills'. But others – both patients and physicians – disagree heartily both with the aetiological assumptions and the practical utility of drugs in these situations.

Even in the management of illnesses about whose legitimacy there is no disagreement, men and women of good will can disagree considerably about the value of treatment. Cancer chemotherapy specialists, I suspect, are a great deal more sanguine about some aspects of their success with drugs than are most non-specialists (or their patients!). The achievement of short-lived objective remission in an elderly patient with acute leukaemia, without impressive benefit in either the length or the quality of life, may for example seem impressive only to the specialist who sees in this a promise of more impressive gains in the future with further empirical manipulation of drugs and dosage regimens.

What, then, do I recommend? Certainly not a diminution in our increasingly effective attempts to quantify adverse effects of drugs. We need to have as good data as possible to deal with the 'cost' (or risk) part of the cost-benefit equation. But we also need to do a proper job with the 'benefit' side. This will require quantification of the short- and long-term improvements in the lives of patients receiving drugs. We shall have to measure 'therapeutic outcome' in the broadest sense of the term, including 'quality of life' and 'activities of everyday living'.

We shall have to study drugs in what I have called the 'naturalistic' setting, i.e. as they are actually prescribed by physicians and taken by patients, with all the vagaries and errors and potential for abuse that exist in this setting. A drug should not be stigmatized by improper use, but we need to know about the latter, if only to be aware of its magnitude, the reasons for it, and possible ways of ameliorating suboptimal usage.

In these efforts, the well-established methodology of the formal controlled trial, which serves us so well when we simply wish to delineate a useful effect, will not be applicable. We shall have to evolve *new* methodologies, and choose the best that we can devise. These methods will not be perfect, but then neither is the controlled trial, or case control studies, or reports of adverse reactions. There is no excuse for not doing the best that we can within the necessary

limits of feasibility and cost.

Finally, however, there is a special problem that presents with drugs not yet on the market, or which have been registered but have as yet been subjected to little in the way of clinical use. There is an increasing tendency to do more and more preclinical testing before clinical experience with a drug is first sought. The hazards of such an approach are two-fold: excessive reliance on the utility and validity of non-human research, and the failure to explore adequately the benefits to mankind of therapeutic application of chemicals.

There are good reasons, for instance, to have doubts about the methods and validity of both mutagenicity and carcinogenicity tests, yet more and more the assumption seems to be that suspicion about the safety of a drug based on such studies requires the prompt assignment of the suspected drug to the Hades reserved for chemicals beneath society's contempt. Yet even with carcinogenicity data much closer to man (as was true for the first three studies linking reserpine to breast cancer) the passage of time and the acquisition of new data may tend to exonerate an innocent drug.

It is one thing to resist hasty and hysterical regulatory decisions to ban a drug when a chemical has been around for a long time (like reserpine and saccharin) and certain benefits are perceived from its use by significant numbers of the population. It is quite another matter when we have to deal with a chemical that has never got out of the animal laboratory, or has been used in only a modest number of patients. In such cases, we can only match up a therapeutic contribution that is like the ghost of the shadow of smoke against the more objective accusations of the toxicologist.

Yet we also know that the therapeutic contributions (like the toxic ones) of a drug are often not adequately known until considerable experience with the drug in humans. The one thing we can guarantee is that the sooner in the life of a chemical it is 'killed', the more likely we are to miss aspects of its pharmacological profile and potential.

No one wants to expose humans to needless risk. We cannot put drugs casually into man. Yet we know that in the past the early study of chemicals in humans with preclinical toxicological testing much more limited than what we do today, turned out to be extraordinarily safe when performed cautiously, by knowledgeable investigators, for short periods of time in small numbers of patients.

The lesson to me seems clear. If a chemical is thought, on the basis of theoretical or empirical pharmacodynamic studies in animals to be a truly promising therapeutic agent, it must not be dropped except for sufficient and adequate cause. The decision to go or not go ahead with human studies should not, and must not, be based on considerations that suggest more the spinal reflex than the frontal lobes. Here, as elsewhere, the more sophisticated is our cost-benefit calculus, the wiser are our decisions likely to be.

Rochester, NY, September 1978.

how to use this book

THE SCOPE OF THE 'ANNUAL'

Side Effects of Drugs Annual is published in January of each year. Up to 1975, *Meyler's Side Effects of Drugs*, the standard reference work, served two functions: on the one hand it provided an encyclopaedic review of all that was currently known on adverse effects and interactions of medicinal substances; on the other hand each edition provided detailed reviews of recent publications in this field. From 1976 onwards these two tasks have been separated. The Annuals now provide each year a detailed and critical account of *new* information in the field, whilst *Meyler's Side Effects of Drugs*, revised editions of which will appear approximately every 3-4 years, will continue to give a general overview of the topic, referring the reader to the Annuals for additional details where necessary. The Annual can thus be used either to complement or update present or future editions of *Meyler*, or as an independent reference work.

SELECTION OF MATERIAL

In compiling the SED Annual particular attention is devoted to those publications which provide essentially new information or throw a new light on problems already recognized. In addition, some authoritative new reviews are listed. Publications which do not meet these criteria are omitted. Readers anxious to trace all references on a particular topic, including those which duplicate earlier work, are advised to consult *Adverse Reactions Titles*, a monthly bibliography of titles from approximately 3400 biomedical journals published throughout the world, compiled by the international Excerpta Medica abstracting service.

PERIOD COVERED

The present Annual reviews all reports presenting significant new information on adverse reactions to drugs from August 1st 1977 up to July 31st 1978. Where possible more recent papers have been included. In each chapter a number of fields in which the situation has changed considerably or in which there are major controversies, are dealt with in depth, referring both to recent and to older literature. Subsequent Annuals will cover the world literature appearing yearly between August 1st of one year and July 31st of the next.

CLASSIFICATION

Drugs are classified according to their main field of application or the properties for which they are most generally recognized. In borderline cases, however, some supplementary discussión has been included in other chapters relating to secondary fields of application. Fixed combinations of drugs are dealt with according to their most characteristic component.

DRUG NAMES

Drug products are in general dealt with in the text under their most usual non-proprietary names; where these are not available, chemical names have been used; fixed combinations usually have no non-proprietary connotation and here trade names have been used as necessary.

SYSTEM OF REFERENCES

References in the text are coded as follows:

R: In the original paper, the point is *reviewed* in some detail with reference to other literature.

r: The original paper *refers* only briefly to the point, on the basis of evidence adduced by other writers.

C: The original paper presents detailed *original clinical evidence* on this point.

c: The original paper provides *clinical evidence*, but only briefly.

The code has not been applied to animal pharmacological papers. The various Editions of *Meyler's Side Effects of Drugs* are cited in the text as SED VII, SED VIII etc.; *SED Annuals 1 and 2* are cited as SEDA-1 and SEDA-2.

INDEXES

Indexing in the Annuals is cumulative over four-year periods, at the end of which the revised *Meyler's Side Effects of Drugs* appears. To obtain complete information on the side effects of a drug, it is therefore sufficient to consult the most recent edition of 'Meyler' and the latest Annual.

The Index of Drugs provides a complete listing of all references to a particular drug in Annuals 1, 2 and 3. The Index of Side Effects is necessarily selective, since a particular side effect may be caused by very large numbers of different compounds; the latter index is therefore mainly directed to those side effects which are acute or life-threatening, those which are discussed in special detail in Annuals 1, 2 or 3, and those which are unexpected. Before assuming that a given drug has not been reported to have a particular side effect, however, the reader should always consult the relevant chapter.

The indexes have been compiled by Dr. H. Kettner, Middelburg, The Netherlands.

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