
Clinical Pharmacology and Drug Epidemiology

3

**Epidemiological
Impact
of
Psychotropic
Drugs**

**G. Tognoni
C. Bellantuono
M. Lader
Editors**

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EPIDEMIOLOGICAL IMPACT OF PSYCHOTROPIC DRUGS

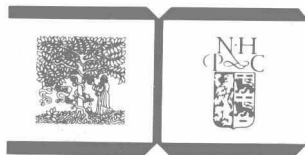
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PREFACE

The modern era of psychotropic drugs dates back 30 years to the discovery of the antimanic effects of lithium and of the neuroleptic actions of chlorpromazine. In those three decades our evaluation of psychopharmacological agents in the laboratory has evolved from fairly simple behavioural and physiological studies to the currently elaborate investigations which link behavioural effects to complex biochemical actions, especially at the receptor sites. Our sophistication has increased also at the clinical level, with rigorous controlled trials complementing the older skills of clinical observation and flair. However, such controlled studies cannot provide much information about the overall effectiveness of psychotropic drugs and how much impact they might have had on day-to-day psychiatric practice.

The epidemiological study of psychotropic drugs can be conducted in various settings. The institution is the most obvious, as much of psychiatric in-patient practice throughout the World is still carried on in these large separate mental hospitals. The impact of neuroleptics on recurrent psychoses, especially schizophrenia, and of lithium on recurrent affective disorders should be apparent there, if these drugs have revolutionised the management of these disorders, as our most enthusiastic colleagues claim. Antidepressants, anxiolytics and hypnotics need to be studied in the out-patient clinics and more important still, in the primary care context. First the anxiolytics and then the antidepressants were tentatively used by psychiatrists and then widely prescribed by general practitioners. And, finally, we await the development of psychotropic drugs to help in the major health problem of the late 20th century in industrialized countries, the great burden placed on our health services by an ageing population with failing mental powers.

Because of the importance of these topics and because very few medical scientific meetings had been devoted to the evaluation of psychotropic drugs using the epidemiological approach, we decided to hold a workshop in the Mario Negri Institute of Pharmacological Research in Milan on June 24th - 26th, 1981. Generous sponsorship of the meeting by the Italian National Research Council (C.N.R.) Grant on Clinical Pharmacology and Rare Diseases and the Lombardy Regional Centre for Drug Information (C.R.I.F.) enabled us to invite a distinguished panel of international speakers drawn from a variety of disciplines.

The first sessions were devoted to the terms of reference of the workshop and to the possible causes of mental illness, genetic, biochemical, viral and social. The patterns and prevalence of psychotropic drug use were then discussed. The evaluation of drugs and therapeutic procedures formed the topic

for the next session followed by an exposition of the methodological problems inherent in the epidemiological approach. Next, the adverse effects of drugs were outlined, with examples concerning tardive dyskinesia, dependence and the special problems of the elderly. The final morning was concerned with the future - new drugs, the usefulness of a multidisciplinary approach, advances in clinical methods and the future of international collaborative studies.

The workshop on the "Epidemiological Impact of Psychotropic Drugs" provided a rare opportunity for the laboratory scientist to discuss problems with the epidemiologist, the clinical psychiatrist to meet the biometrician. We hope that publication of the papers given at the workshop will stimulate further fruitful interchange of ideas.

Malcolm LADER

Gianni TOGNONI

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INTRODUCTION: THE TERMS OF REFERENCE

Michael Shepherd

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I must admit to feelings of gratification at the title and objectives of this meeting. Their origins go back some 15 years to when Professor Lader, Professor Rodnight and I were preparing what proved to be the first textbook of psychopharmacology, which subsequently appeared in an excellent Italian translation by Professor Valzelli of this Institute (1). The problems facing the author of a first textbook of a new discipline concern form as well as content. In this case I decided to include a brief section devoted to the epidemiological aspects of drug treatment in the final chapter on the implications of psychopharmacological research, for even then it was apparent that the topic was destined to assume increasing importance. And so it has proved.

Epidemiology, which means literally no more than 'on the people', is the medical science which takes the population or aggregate, and not the individual, as the unit of study. Its prime concern is with the associations rather than the mechanisms of disease and its methods can be adapted to study causal factors, clinical diagnosis and outcome (including therapeutic assessment) and the workings of health services. It was very rarely mentioned during the earlier years of the psychopharmacological era, which was dominated by a sense of confident expectation: the publications on basic science were dominated by the optimistic claims of the laboratory workers, while the clinical field was flooded by enthusiastic, if mostly uncritical, reports. The word 'epidemiology' appeared mostly in its adjectival form with a pejorative colouring, 'epidemiological scepticism', a term which was introduced by Freyhan in the 1960's and repeated mindlessly by clinicians who were seemingly unaware that a sceptic is merely a man who seeks to know. Let me take one relevant example. One of the principal targets selected for adverse comment was the

controlled clinical trial, an essentially epidemiological procedure designed to compare populations identical in every respect but the modality of treatment under investigation. In psychiatry a landmark was achieved in 1965, when the Medical Research Council of Great Britain published the results of its large-scale trial of the treatment of depression(2). Shortly afterwards I presented the results of this study here at the Mario Negri Institute during the 1st International Symposium on Antidepressant Therapy. My paper attracted the following, self-explanatory comment from a discussant: "Such an approach carries on the worst possible tradition of drug use. To gild this procedure with double-blind techniques and statistical analysis cannot overcome its limitations which restrict the value of the conclusions which can be drawn (3)". Such was the climate of opinion at the time.

Even in the more sober decade of the 1970's the epidemiological viewpoint has not figured prominently in the psychopharmacological literature. Dr. Bellantuono and his colleagues have given numerical expression to this fact by scanning four prominent psychiatric journals from 1977-1979 in search of papers on seven related topics: drug monitoring, drug utilisation patterns, long-term evaluation of drug treatment, short versus long hospitalisation, comparability of diagnosis, evaluation of institutional organisation and psychiatric epidemiology (4). The proportion of published papers dealing with these topics was only 5.4%, though it is, I think, worth pointing out that this figure would have been higher if the search had been conducted elsewhere. In one reputable British journal devoted to research in psychiatry and the allied sciences, for example, some 33% of the 242 papers published during this period were devoted to these matters and of these a substantial proportion were focussed on the titular theme of this conference, namely the impact of psychotropic medication. Since particular areas of the epidemiological spectrum are to be explored in detail by other speakers in the next two days I should like to concentrate directly on this topic, which may be sub-divided into two broad categories: one is concerned with the impact of drugs on hospital populations and the other with their impact on extra-mural mental disorders. I will take each in turn.

HOSPITAL POPULATIONS

The most striking effect of psychotropic drugs on one section of the psychiatric population was already evident enough to have been summarised in our textbook as follows:

"The encouraging results of pharmacotherapy in the treatment of mental illness have had social and administrative as well as therapeutic repercussions for psychiatry. This has been particularly true of the management of schizophrenics with the phenothiazines. It has been argued that if drug therapy can result in the more rapid improvement of acute schizophrenia and can facilitate the rehabilitation of chronic schizophrenics, then the need for large custodial institutions would diminish." (5)

This argument is still to be heard today. The recently published 'Clinical Handbook of Antipsychotic Therapy', for example, is advertised as "a long-awaited guide to anti-psychotic drugs, which are primarily responsible for the revolution in mental health care during the past quarter century. On any given day, at least one million patients are taking anti-psychotic medication and, as a result of the use of these drugs, the prognosis for psychotic patients, formerly warehoused in the back wards of mental hospitals has improved tremendously". (6)

A closer examination of the facts, or rather the figures, suggests that this represents an over-simplification of a complex phenomenon. One alternative explanation emerged from a study which I carried out several years ago on a single mental hospital providing in-patient care for a whole district which I had been able to study over several decades (7). Here I concentrated on the hospital population over a 4-year period extending from 1954 to 1957, i.e. from the year before the introduction of psychotropic drugs to a year in which they were extensively prescribed (8). The results of a study of this type, I would point out, depend on detailed statistical analysis and they showed that very little change had occurred during this period. The major movement of the hospital-population, defined in terms of a higher discharge-rate and a shorter hospital-stay, had in fact

taken place 10 years earlier and was attributable partly to the somatic treatments of the day but much more to the setting up of an unusually progressive mental health service in the area. A very similar pattern was reported independently by Ødegaard in Norway who drew the seemingly paradoxical conclusion, that "in hospitals with a favourable situation the psychotropic drugs brought little or no improvement or even a decrease in the rate of discharges. In hospitals with a low pre-drug discharge rate, on the other hand, the improvement was considerable" (9). Reviewing these and other related findings shortly afterwards Sir Aubrey Lewis put the matter bluntly: "If we had to choose between abandoning the new industrial resettlement units and other social facilities available to us, there would be no hesitation about the choice: the drugs would go" (10).

Behind this disagreement on the seemingly remote question of administrative statistics there lay, and still lies, a profound difference of opinion concerning the specificity of pharmacotherapy. On the one side are those workers who view mental disorders in essentially biological terms, regard psychotropic drugs as curative and speak of anti-psychotic action; on the other side are those workers who see the diseases in multifactorial terms, assess the drug-effects as primarily symptomatic and pay particular regard to the non-specific factors in therapy. It is this latter group who, by and large, have adopted the epidemiological standpoint.

Assessing the extent of disease

With the increasingly widespread assumption that most forms of mental disorder respond to psychotropic medication it has been argued that the frequency of the illness might be estimated from therapeutic data if specificity of treatment can be assumed. This approach has been adopted in the case of lithium, which has been taken by Eastwood and his colleagues in Toronto as an index of the size of affective disorders on the grounds that "the prescription of lithium is more specific than for most drugs in the psychiatric pharmacopoeia, particularly when the patient has

shown evidence of mania" (11). The Canadian workers have attempted to arrive at an estimation of the one-year prevalence rate by obtaining information from a survey of practicing physicians concerning the numbers of their bipolar patients in treatment and comparing the result with those from two indirect methods, namely the total number of serum lithium estimates performed in a large urban area and the total amount of lithium carbonate sold in that same area. The results were strikingly similar - 1.86, 1.83, and 1.21/1000 respectively - and led to the suggestion that such indirect methods might be employed for trend-analysis over time, a statistic which carries even more significance for epidemiological inquiry.

Such a study has in fact been carried out recently by Symonds and Williams who have examined the use of lithium carbonate in relation to English mental hospital data during the years 1970-75, suggesting that "...the introduction and dramatic increase in the use of lithium salts would, relative to all admissions, markedly decrease. Furthermore, it would be expected that this effect would be manifest principally with second and subsequent admissions to hospital, as the probability of an individual with affective disorder being treated with lithium without previous admission is low" (12). In the event it emerged that a massive increase in the use of lithium compounds was accompanied not by a decrease in the hospital admissions and re-admissions with mania but by an increase, which at face value does not support the notion of effective prophylaxis. However, three alternative explanations have to be considered: an increasing frequency of manic disorder, an increasing readiness to admit such illnesses to hospital and a change in the diagnostic habits of clinical psychiatrists. An examination of these competing hypotheses, all of them susceptible to epidemiological inquiry, is therefore necessary before accepting the widely propagated view that the lithium ion exerts a specific action on the pathophysiology of manic illness.

Monitoring therapeutic activity

The development of refined laboratory techniques for the estimation of psychotropic drugs in biological fluids, especially plasma, has led to a wave of interest in the possibility of applying pharmacokinetic principles to the study of therapeutic effects. The value of this type of investigation has still to be demonstrated in most neuropsychiatric disorders, with the possible exception of epilepsy. On the other hand, the delineation of adverse effects in large populations has already produced useful results. A good example of the method is the report from the Drug Epidemiology Unit and the Boston Collaborative Drug Surveillance Program on the induction of bone-marrow depression by phenothiazines (13) which involved the screening of three large, separate populations: 1048 psychiatric in-patients, 18,587 medical in-patients and a mixed group of 24,795 medical, surgical and gynaecological patients. In addition to the drug-history information was collected about sex, age, diagnosis and duration of therapy. The analysis showed no relationship between leucopenia and phenothiazines in a large group of patients in either psychiatric or general hospitals. A more significant problem is the vexed question of tardive dyskinesia, where definitions are less clear-cut and the reported prevalence among hospital populations has varied between 5 and 50%(14), a problem which Dr. Klawans will be discussing later in the meeting.

EXTRA MURAL POPULATIONS

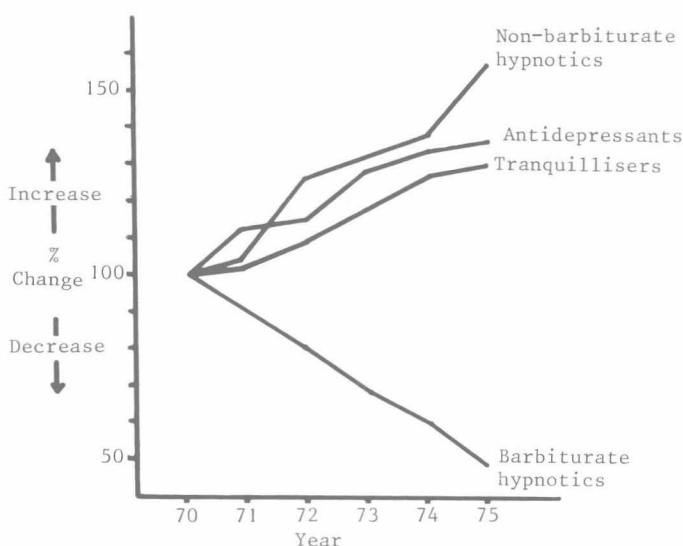
It has been demonstrated repeatedly that while the pharmacotherapy of hospitalized patients may be effective in the control of symptoms, the discharge-rate is merely an administrative index which can conceal extra-mural clinical and social realities. A prominent advocate of long-acting, injectable neuroleptics, for example, has attributed 4 benefits to these drugs: (1) that they facilitate the return of patients to the community and their maintenance therein; (2) that they help the patient's family by ensuring drug-compliance; (3) that they favour the processes of rehabilitation; and (4) that they constitute an economy of time and resources(15). Such dogmatic claims have not, unfortunately,

been fully supported by more objective investigations of the fate of patients discharged from hospital. All too often the impact of the medication is what Pasamanick in one of the earliest controlled investigations of schizophrenics in the community accurately described as "the transfer of the mental hospital atmosphere to the community" (16). Several subsequent studies of the outcome of schizophrenic patients receiving long-term continuation therapy after discharge from hospital, including our own (17), have lent support to the conclusion reached by Stein in a recent review, namely that "Although hospitalisation may have undesirable effects on patients, there may be greater patient harm and certainly greater burden to the community if use of hospital is denied on 'principle' without providing adequate community programming in its place" (18). The Italian experience, about which we shall be hearing, is clearly relevant and must be evaluated in this context.

The major impact of psychotropic medication on extra-mural mental disorder, however, has less to do with the more severely ill patients who are returned to the community from hospital than with the much larger population of patients who rarely, if ever, make contact with the mental health services. The clearest index of events has been the striking increase in prescription-figures of certain groups of psychotropic drugs. Whereas, as we shall see, the precise significance of this phenomenon remains uncertain, it has undoubtedly brought psychopharmacology into the main body of medicine and has involved most of all its general practitioners. This emerges immediately we address ourselves to the question of not only the quantity of drugs prescribed but also who does the prescribing, for which conditions and with what purpose. The broad picture that emerges is consistent in all those countries from which data have been published.

In the United Kingdom, by way of illustration, there has been a rise in the prescription of what the British Department of Health and Social Security calls 'tranquillizers' and 'non-barbiturate hypnotics', principally the benzodiazepines - chlordiazepoxide, diazepam and nitrazepam - over the quinquennium 1970-75 (Fig. 1).

Percentage change in psychotropic drug prescription
in England, 1970-1975 (1970=100%)



During this period there was also a clear rise in the consumption of the 'anti-depressant' drugs, amitriptyline and imipramine, and a fall in the prescription-rate of barbiturates. A similar picture comes from the United States, where Mellinger and his colleagues have reported the findings of the National Disease and Therapeutic Index, a reporting service which monitors the medical behaviour of a national sample of physicians in private practice (19). In the early 1970's on the basis of an examination of the pharmacological treatments of new out-patients, they reported that general practitioners were responsible for half the prescription of psychotropic drugs. The proportion prescribed by psychiatrists, by contrast, was no more than 5%, a figure which rose to only 17% even when chronic conditions were included. Much the same trend emerged from the survey by Parry and his colleagues of 7 other European countries (20).

A heightened awareness of the need to recognise and treat depressive disorders largely explains the increase in the prescribing of the anti-depressant drugs. In the United Kingdom, for example, two National Morbidity Surveys conducted in 1955/6 and