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Development of a registry for monitoring psychotropic drug prescriptions: aims, methods and implications for ordinary practice and research

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Abstract

In psychiatry, individual-based registries have provided key information on risks and benefits associated with the use of psychotropic drugs but they have rarely been employed for monitoring and evaluating the everyday prescribing of psychopharmacological treatments. This article describes the cultural background that gave impetus to the idea of registering all prescriptions of psychotropic drugs dispensed by physicians working in the South Verona community mental health service, and presents the methodology employed to develop such a registry in a community psychiatric service where a psychiatric case register (PCR) has been operating since 1978. We developed a registry including every patient receiving psychotropic medications in ordinary practice. This registry is linked to the PCR in order to obtain data on social and demographic characteristics, clinical symptoms, diagnosis, use of services, and outcomes. No exclusion criteria are allowed – anyone receiving treatment is automatically included. This system, which can link drug and service-use data with hard outcome indicators, can generate information on the proportion of subjects discontinuing treatment, switching medication because of side-effects, recovery or inefficacy, as well as on the proportion of subjects failing to return to the physician, and the proportion of patients who improve. The innovative aspect of this approach is that this registry is developed, organized and used by physicians interested in monitoring their clinical practice and in providing patients, relatives and the public with accurate information on drug use in their specific context of care.

Key words: epidemiology, psychotropic drugs, prescription databases

Terms of reference

In recent decades advances in technology have led to an increase in the number of individual-based registries (Sorensen et al., 2001). These registries, developed for management, claims, administration and planning, cover large groups of individuals and generate data that are of value in pharmacoepidemiological research. Pharmacoepidemiology studies the use and the effects of drugs in a large number of people (Grasela, 1996; Bergman, 2001). Classical uses of these registries include the identification of adverse effects of psychiatric medications, such as, for example,

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the association between second-generation antipsychotics (SGAs) and metabolic abnormalities, or the identification of unanticipated benefits from psychiatric medications, such as, for example, the potential benefit of clozapine against suicidal behaviour (Jick et al., 1998; Wang et al., 2003).

Interestingly, although in psychiatry individual-based registries have provided key information on risks and benefits associated with the use of psychotropic drugs, they have rarely been employed for monitoring and evaluating the everyday prescribing of psychopharmacological treatments (Barbui et al., 2002). In contrast, in other fields of medicine such registries have already been developed and extensively employed to answer many different research questions. Key examples are the prescription-event monitoring system pioneered by the Drug Safety Research Unit in Southampton (Inman and Pearce, 1993), and the UK general practice research database (Hennessy et al., 2004), which monitors drug use and outcomes in large and unselected populations of general practice patients. In psychiatry, given the well recognized and documented gap between recommendations derived from experimental studies and the everyday use of drugs (Laupacis et al., 2003), the development of pharmacoepidemiological registries for monitoring drug prescriptions represents an opportunity for auditing the quality of prescribing, for identifying special groups of difficult-to-treat subjects and for highlighting epidemiologically relevant populations of patients systematically excluded from experimental studies. It also represents an opportunity for monitoring the probabilities of different outcomes under real-world circumstances, and for studying variables that might affect outcome (Black, 1999).

The purpose of this article is to describe the cultural background that gave impetus to the project of registering all prescriptions of psychotropic drugs dispensed by physicians working in the South Verona community mental health service, and to present the methodology employed to develop such a registry in a community psychiatric service where a psychiatric case register (PCR) has been operating since 1978. Its expected benefits and implications for ordinary practice and research will be discussed.

Cultural background

In Italy, before 1978, mental health care was centred on the mental hospital. After the implementation of the 1978 Mental Health Act, mental health care was centred on community psychiatric services. In South Verona, a catchment area located in the north of Italy, the main agency providing psychiatric care for the adult population is the South Verona Community Mental Health Service. This is a unitary service, in which great emphasis is given to communication between all staff members and to integration between the various clinical activities. It comprises one inpatient unit located in the general hospital and a network of outpatient and community facilities (Tansella et al., 1998). The inpatient unit is an open ward of 16 beds located in the academic general hospital, which has about 1,000 beds. It is a traditional hospital ward, similar to all other medical wards in the hospital, and patients can be admitted on a voluntary or compulsory basis.

The style of working privileges a psychosocial approach, with a strong emphasis on continuity of care and rational drug use (Tansella and Burti, 2003). To assure continuity of care, inpatients are treated by the same clinical team that provides outpatient community care, and pharmacological treatments, dispensed during the acute inpatient phase, are usually continued at discharge. In addition to psychotropic drugs, a comprehensive system of outpatient community interventions, based on patients' needs, are usually developed and implemented after the admission episode. During the last 25 years the community service gradually developed: more staff was available for outpatient and community care, and rehabilitative activities increased. On the other hand the number of hospital beds remained stable (Tansella et al., 1998).

A PCR has been operating since 1978 in this area (Amaddeo et al., 1997). The local system of psychiatric care is an ideal setting for implementing and using PCRs, because individuals with psychiatric problems living in a specific catchment area are followed by the psychiatric service of that area; subjects seeking psychiatric care outside the catchment area are always referred to their catchment area. In this system, PCRs routinely and prospectively collect service use data on unselected populations of typical patients seeking psychiatric care. The South Verona PCR routinely records, for all subjects in contact with the psychiatric service, sociodemographic characteristics, ICD-10 diagnoses, past psychiatric and medical history, clinical data, admissions and outpatient contacts. The PCR

also records details of patients who leave the catchment area, and those who die.

The PCR is used for clinical, administrative and research purposes, with the underlying rationale being that health services must provide accurate, routinely collected data on their clinical activities and outcomes, in order to evaluate them and to make them accountable. The PCR, however, does not routinely collect information on prescriptions of psychotropic drugs, and therefore no accurate, routinely collected data on this specific sector of clinical activity were available. This lack of information gave impetus to the project of developing a registry for monitoring psychotropic drug prescriptions in an innovative way, including every patient receiving psychotropic medications in ordinary practice. Such a registry had to be linked to the PCR in order to receive data on social and demographic characteristics, clinical symptoms, diagnosis, use of services, and outcomes. No exclusion criteria had to be allowed; anyone receiving treatment had to be automatically included. Information on the proportion of subjects discontinuing treatment or switching medication because of side effects, recovery or lack of efficacy, had to be generated, as well as information about the proportion of subjects failing to return to the physician, and the proportion of patients who improve. The innovative aspect of this approach is that this registry had to be developed, organized and used only by physicians interested in monitoring their clinical practice and in providing patients, relatives and the public with accurate information on drug use in their specific context of care. In this framework, the presence of a monitoring system able to link drug- and service-use data with hard outcome indicators was though to be the first quality requirement for physicians who want to hold themselves as accountable.

Objectives and aims

In an effort to fill this lack of data, we developed and implemented a system for monitoring psychotropic drug prescriptions on a routine basis. Within the framework of the Dipartimento per la Valutazione dei Medicinali of the Italian Ministry of Health, which financially supported the project, we designed a registry with the following characteristics:

- comprehensive and flexible, allowing physicians to access it during clinical work to get a detailed pharmacological history of every patient in contact with the service, and to get information on any reasons which led to stopping or changing previous medications;
- easily accessible from different places simultaneously, meaning that different physicians seeing patients in different facilities have the possibility of accessing it at the same time;
- time saving, meaning that physicians have the possibility of updating every pharmacological treatment they prescribe very quickly;
- exportable, meaning that the Italian Ministry of Health wanted us to pilot a system that could be transferred to other psychiatric care contexts.

In addition to these clinical uses, we developed a registry storing a minimum set of information to be used for auditing purposes and for research. Linking this registry with the PCR, at least seven indicators of prescribing can be calculated for a given period of time:

1. Rate of subjects receiving psychotropic drugs.
2. Rate of subjects receiving combined treatments.
3. Rate of subjects receiving off-label prescriptions.
4. Rate of subjects receiving treatments for adequate time.
5. Rate of subjects receiving adequate dose regimens.
6. Rate of subjects withdrawing/changing medication because of adverse effects/recovery/inefficacy.
7. Rate of subjects experiencing adverse effects.

The psychotropic drug registry

The registry was developed in 2003 and a piloting phase started at the beginning of 2004. Using a IBM system (Server NETFINITY 5100, with three harddisks 9.1 GIGA Hot Swap), we designed a registry operating with WINDOWS 2000 and with MySQL 4.1 as the relational database. This system allows access to the registry using most Internet browsers. In practical terms this means that from any personal computer located within the service it is possible to access and use the registry with a standard Internet browser. The first Web page of the registry reports the name and the personal identification number (patient code), the ICD-10 diagnosis and a list with all treatment regimens currently prescribed. For each prescription, the date of prescribing, the number of units (tablets, drops, injections) prescribed and the time when the medication should be taken (morning, lunch, afternoon,

evening, night, as needed) are recorded. If a medication is stopped, a final date is recorded, and a new window asks the prescriber the reason(s) for stopping that specific medication.

The system works in such a way that physicians, when prescribing a medication for the first time, store that prescription in the registry. During the following outpatient contacts, physicians do not need to add any further information, or modify the existing information, if the therapeutic regimen remains unchanged. However, if a prescription is stopped (or increased/decreased) the registry needs to be updated, as well as if a new prescription is issued to that specific patient.

Three fundamental elements interact in this registry: patients, prescribers, and prescriptions. The basic structure of the registry is the medication record. When a specific medication is prescribed, the corresponding record automatically stores the anatomical therapeutic chemical code, the generic name and the defined daily dose (DDD) of that medication. In this registry a crucial issue is the conversion of each medication dosage into a standard measure allowing calculation, for each patient, of a cumulative index of drug exposure. A widely used system employs the chlorpromazine equivalents methodology, but this can be applied to antipsychotic drugs only. We therefore decided to adopt the defined daily dose (DDD) methodology. This measure is the international unit of drug use approved by the World Health Organisation (WHO) for pharmacoepidemiological studies (WHO, 1996). The DDD is a theoretical unit of measurement defined as the assumed average maintenance daily dose for a drug, used for its main indication in adults. For each new therapeutic agent introduced in the market, WHO calculates the appropriate DDD, and a list of all medications with the corresponding DDDs can be accessed at www.whocc.no/atcddd. It is therefore possible to convert psychotropic agents' daily doses, in milligrams, into multiples of the DDD by dividing the prescribed daily dose (PDD) by the DDD (PDD/DDD) (WHO, 1996; Barbui et al., 2002). A ratio of one indicates that the dose prescribed is equal to the DDD of that drug; a ratio greater than one indicates a dosage higher than the standard dose, while a ratio lower than one means a low dose.

Table 1 illustrates how data are stored. In the example, four records store information on three patients. The column 'start' indicates when the medication was started. The column 'end' is empty for those medications still under prescription. In the example, patient number 1 is currently receiving two drugs. The first record indicates that patient 1, every 15 days (column 'frequency'), is receiving a half injection (column 'units') of long-acting fluphenazine 25 mg. It is possible to calculate the PDD, in milligrams, using the following formula: (mg × units × day) / frequency, where mg is the quantity of drugs, in milligrams, contained in each unit (tablet, drop, injection); units is the number of tablets, drops, injections administered; day is the number of administrations during the day; frequency indicates the number of days between two administrations. In this example the PDD is: (25 × 0.5 × 1) / 15 = 0.83 mg (PDD). This figure can now be converted into multiples of DDD: 0.83 / 1 = 0.83. This means that fluphenazine was administered at a PDD slightly below to its DDD.

According to local regulations, no formal approval by the local ethics committee was required for implementing this registry, given its descriptive nature. Moreover, no specific written informed consent was obtained because all patients routinely provide consent for their clinical records to be used for

Table 1. Structure of the psychotropic drug registry

Patient code	Medication	Start	End	ATC	Mg	DDD	units	day	frequency
1	Fluphenazine 25 mg long-acting	1/1/04	–	N05AB02	25	1	0.5	1	15
1	Amitriptyline 25 mg capsules	1/1/04	10/2/04	N06AA09	25	75	2	2	1
2	Lorazepam 1 mg tablets	1/2/04	–	N05BA06	1	2.5	1	3	1
3	Haloperidol 0.2% drops	1/3/04	–	N05AD01	0.1	8	10	3	1

The shape of data is 'long', that is each prescription is represented by a record and the subject identifier is repeated. However, for some statistical analysis it is possible to create one single vector containing all prescriptions for each patient, the so called 'wide' shape.

epidemiological and research purposes, when full confidentiality is ensured.

Using the registry for auditing purposes and for research

The routine collection of data on therapeutic agents prescribed in ordinary practice generates a massive amount of secondary data. Secondary data are data that have not been collected with a specific research purpose (Sorensen et al., 2001). A key factor in the use of these data for auditing and research purposes is the definition of a minimum set of possible analyses, and the recognition of some limitations. The remainder of this section describes some of these possible uses. A general limitation of this system is the lack of data on whether patients eventually took the prescribed agents, since data have consistently shown that a relevant proportion of the medicines prescribed for people with chronic conditions are not taken (Jones, 2003).

Trends and predictors of psychotropic drug use in ordinary practice

A very simple auditing tool is the comparison of how psychiatric medications are used in different index years. This provides interesting insights on changes over time in the way physicians treat patients with serious mental disorders. In the piloting phase of this project we used the psychotropic drug registry to collect data retrospectively on drug use at patient discharge in three different index years (Barbui et al., 2004). All patients consecutively admitted to the inpatient unit during the years 1981/1982, 1991/92 and 2001/02 were identified using the PCR, and using the psychotropic drug registry all psychotropic drug prescriptions at discharge were recorded. During the six years surveyed 160 patients were admitted in 1981/82, 139 in 1991/92 and 228 in 2001/02. An increasing proportion of subjects receiving antipsychotic, antidepressant and benzodiazepine treatment at discharge was observed. In addition, we found an increasing proportion of patients receiving two or more psychotropic drugs at discharge, which accounted for almost 80% of cases in 2001/02. The number of psychotropic agents prescribed at hospital discharge was positively correlated with the total consumption of psychotropic drugs. A relevant proportion of patients was also given agents for medical conditions, yielding an average number of 3.2 prescriptions in 2001/02. The Lavik score, a summary index of service use, indicated that subjects admitted in 1981/82 were moderate users of psychiatric services, while those admitted in 1991/92 and in 2001/02 were high users of psychiatric services, thus suggesting that drug and service use showed similar trends over the years.

Off-label prescribing

These pilot data were also used to assess the degree of coherence between diagnostic categories and drug prescriptions. In Europe regulatory authorities routinely assess new drugs' marketing authorization applications and release them for marketing with licensed indications (Barbui et al., 2001). Licensed indications for antipsychotic drugs limit their use to specific psychiatric disorders. We linked the psychotropic drug registry with the PCR to calculate the proportion of *off-label* antipsychotic prescribing, that is the proportion of prescriptions issued outside the licensed indications. Findings showed that nearly 50% of second-generation antipsychotic prescriptions were for an off-label indication (Barbui et al., 2004). In contrast, less than 15% of first-generation antipsychotic prescriptions were for an off-label indication. Approved labels for first-generation agents explain these findings, since they cover a much broader range of indications than any of the new agents; however, this off-label use has consequences. In Italy it implies that doctors take the full responsibility for the prescription and that patients give informed consent and pay the full price of the drug, since reimbursement is restricted to disorders stated in the label.

Longitudinal patterns of drug use

A crucial step forwards in the use of drug registries will certainly be the possibility of following cohorts of subjects receiving similar drug treatments longitudinally (McMahon and MacDonald, 2000), and to study whether different patters of drug use act as determinants of patient outcomes. In ordinary practice, for example, it would be of interest to establish whether the safer side-effect profile of second-generation antipsychotics in comparison with first-generation antipsychotics, detected by experimental studies, determines better treatment adherence in practice (Dolder et al., 2002). Data stored in the psychotropic drug registry could be used to extract cohorts of subjects starting treatment with first- and second-generation agents; these subjects could be followed longitudinally under real-world circumstances with the aim of calcu-

lating whether those receiving second-generation agents are more adherent to treatment. We still do not have consistent data showing that, in ordinary practice, newer agents are associated with better patient adherence and, more important, we still lack data showing a positive association with patient outcome. In this system, the contributing role of adverse effects could be studied in relation to treatment adherence.

Populations missed by experimental studies

The most interesting way of using the psychotropic drug registry consists in recognizing patient populations systematically missed by experimental studies. In recent years, for example, analyses of general practice prescription databases provided stimulating insights (Rosholm et al., 2001; Pietraru et al., 2001; Barbui et al., 2003). First, these analyses showed that most antidepressant prescriptions were issued by general practitioners and not by psychiatrists; second, the use of these agents progressively rose with the increasing age, yielding very high prevalence rates in old and very old subjects. The former information was expected but the latter wasn't because most epidemiological studies demonstrated that the prevalence of depression does not greatly increase with the advancing age. In late life, moreover, antidepressive agents with sedative properties were usually used, whereas in young and adult people 'activating' agents were more frequently prescribed. Third, the proportion of subjects receiving other medicines, in addition to psychotropic agents, was generally high, and progressively rose in the elderly. Prescription databases can thus be used to identify clinically relevant grey areas, in this case constituted by elderly subjects, followed by general practitioners, suffering from medical conditions requiring the use of medications, and suffering from depressive symptoms which probably do not fulfil current criteria of major depression. Intriguingly, these patient characteristics exactly correspond to clinical trial exclusion criteria, where subjects older than 65 years are usually not included, those taking medicines for medical conditions are never studied, and those with mild depressive symptoms are considered epidemiologically less important than those suffering from major depression (Posternak et al., 2002; Zimmerman et al., 2002; Keitner et al., 2003).

Concluding remarks

The presence of monitoring systems, able to link drug and service-use data with hard outcome indicators, should be seen as a basic quality requirement for modern psychiatric services. The underlying rationale for developing a psychotropic drug registry should be the interest in monitoring ordinary practice and for providing patients, relatives and the public with information on drug use and patient outcomes. For example, it might offer a tool for comparing medication prescribing patterns with recently published expert consensus guidelines for medication treatment of psychiatric disorders, thus supporting audits of clinical practice and optimizing psychiatric medication use. A research attitude among physicians would also be stimulated, thus helping discover areas of clinical uncertainty (Naber and Pincus, 2003). In such areas the possibility of conveying this uncertainty into the rules of a pragmatic clinical trial should be carefully considered (Hotopf et al., 1999), thus making the practice of medicine a prerequisite for generating experimental evidence.

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