

Pharmaco-epidemiology: what do (and don't) we know about utilisation and impact of psychotropic medications in real-life conditions?

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Studies have confirmed the often large differences that exist between the conditions of pre-marketing trials and those of actual practice several years into the market life of a pharmaceutical product (Martin *et al*, 2004a). A clinical trial is necessarily based on a small sample of people selected from the source population by inclusion and non-inclusion criteria in order to reduce inter-individual variability. These people are usually treated with a fixed protocol, specifying dosage, duration and concomitant medications. Pre-marketing data must therefore be complemented by a field assessment to measure any eventual distortions and to estimate their consequences on real-life effectiveness and safety. Pharmaco-epidemiology is an interface discipline that can be defined as the study of the interactions between drugs and populations (Bégaud, 2000). Its objective is to assess the utilisation and impact (benefit and risk in 'real life' conditions) of health care products at the level of the population actually treated, not just on the theoretical target population as defined by pre-marketing trials and marketing authorisation. Although they follow the three classical areas of epidemiology (cross-sectional, prospective or retrospective studies), pharmaco-epidemiological studies have to handle the specific problems associated with drugs, such as multiform and unpredictable risk, sometimes very low incidence rates, dynamics and variability of exposure, and large number of drugs available on the market. This has justified the development of adapted pharmaco-epidemiological approaches, such as spontaneous reporting, case–population studies, case–crossover and case–time designs. The pharmaco-epidemiological approach has already been fruitfully applied to the investigation of the prescription of psychotropic medications at the population level; however, this field of research needs to be further developed owing to the large number of medical, ethical and economic questions

raised by the extensive and expanding use of psychotropic drugs.

UTILISATION STUDIES

Discrepancies between clinical trials and utilisation in naturalistic conditions need to be identified because of their potential clinical and economic impact. These discrepancies may concern prescription characteristics associated with lower efficacy (e.g. insufficient dosage or duration) or with increased risk of adverse effects (e.g. hazardous co-prescription). The gap between guidelines and utilisation is well established for psychotropic medications commonly prescribed by primary care practitioners, such as antidepressants (Donoghue & Hylan, 2001). However, this gap is also noticeable for drugs assumed to be mainly prescribed by specialists, such as antipsychotics (Barbui *et al*, 2002). Using the French social security insurance database, we found that the prescription pattern of risperidone was characterised by a high level of concomitant drug prescription (Martin *et al*, 2004b). In particular, antidepressants were co-prescribed in 43% of patients treated with risperidone, although the efficacy and safety of such co-prescription has been insufficiently investigated in clinical trials. An anticholinergic drug was co-prescribed in 19% of the people studied (16% of those treated with a dosage of less than 6 mg), suggesting that the marketing claim of a low incidence of extrapyramidal side-effects with risperidone prescribed at recommended dosage might not be confirmed in naturalistic conditions.

Utilisation studies are also fundamental to identifying possibly unfounded or hazardous extensions of the indications for psychotropic medications. The widening of the boundaries of treatable illness, often favoured by the marketing pressure of pharmaceutical companies, is not specific to psychiatry (Moynihan *et al*, 2002), but it is a

phenomenon to which the specialty is particularly vulnerable; uncertainty regarding the boundaries between normality and caseness allows the creation of new diagnostic categories of putatively treatable psychiatric disorders. An example of a potentially hazardous extension of indication can be drawn from community surveys showing that a large percentage of children and adolescents treated with psychostimulant drugs do not fulfil the diagnostic criteria for attention-deficit hyperactivity disorder (Rey & Sawyer, 2003). Early intervention in psychosis provides an illustration of extension of indication generated by the creation of a new diagnostic category with need of care. Owing to the lack of valid screening tests, it is not yet clearly established at the population level whether the benefits of antipsychotic medication in people with preclinical psychosis are superior to the risks linked to unjustified prescription in cases with a false-positive diagnosis (Verdoux & Cougnard, 2003). However, it is striking that interest in early intervention markedly increased when new antipsychotic drugs became available, and the enthusiastic support of early intervention programmes by pharmaceutical companies suggests that they at least have little doubt about the benefits they can obtain from this strategy. The current promotion of the use of antipsychotics not only in preclinical psychosis but also in bipolar disorder and behavioural disturbances of dementia may reassure prescribers about the safety of these drugs, inducing their even more widespread use. It is thus necessary to explore at the population level whether the utilisation pattern of these drugs is altered, not only in psychiatric settings, but also in primary care. Several other examples could be given for each class of psychotropic medication, pointing to the need for studies examining utilisation patterns in naturalistic conditions in order to identify discrepancies between guidelines based on clinical trials and actual use.

OUTCOME STUDIES

Although clinical trials may identify the most frequent adverse effects associated with the use of psychotropic medications, they are of limited value in detecting delayed or less prevalent risks linked to exposure to a new drug. Such adverse reactions have to be identified as early as possible, since even a small increase in risk may

have a serious impact on the health of the population if many people are exposed to the drug. Surveillance by centralised pooling of spontaneous reports facilitates the detection of previously unidentified drug-related risks, which can be subsequently confirmed or dismissed by field and database studies. The availability of population-based databases documenting drug exposure is therefore crucial for the identification of risks associated with psychotropic drug use. Such databases have the advantage of meeting a major need in pharmaco-epidemiology – the observational nature of the data. Furthermore, studies using these databases are less prone to selection bias, and are therefore more representative, than pre-marketing clinical studies. Examples of such studies include the use of the UK General Practice Research Database to document the risk of diabetes in people treated with new antipsychotics, which provided strong evidence that the risk was higher for olanzapine than for other antipsychotics (Koro *et al*, 2002).

Another major issue addressed by outcome studies is the risk of psychiatric disorders induced by prescription of psychotropic or non-psychotropic drugs. A further example of the usefulness of population-based studies is provided by the debate on the suspected link between autism and exposure to the measles, mumps and rubella triple vaccination. Findings obtained in clinical samples of uncertain representativity generated a huge scientific controversy, widely amplified by the media. There is now strong evidence against this hypothesis, as rigorous population-based studies have failed to find such an association (DeStefano & Thompson, 2002; Madsen *et al*, 2002). A markedly under-developed field of investigation concerns the delayed psychiatric risks associated with psychotropic use; for example, the possible risk of dementia associated with exposure to benzodiazepines needs to be further explored owing to the public health consequences of such a finding (Lagnaoui *et al*, 2002).

Another major public health issue concerns the psychiatric consequences of medication prescription during pregnancy. Although the association between exposure to perinatal risk factors and increased vulnerability for psychiatric disorder is well documented, knowledge is strikingly sparse regarding the impact of prenatal exposure to prescribed drugs on the delayed risk of psychiatric disorder (Verdoux, 2002).

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Owing to their methodological limitations, no definite conclusion regarding behavioural teratogenicity can be drawn from most studies exploring the risk associated with prenatal exposure to psychotropic medication (Walker *et al*, 1999). Sparse findings suggest that exposure to xenoestrogens such as diethylstilbestrol may be a risk factor for psychiatric disorders, mediated by a possible deleterious impact of these substances on foetal neurodevelopment, but this hypothesis is speculative owing to the small number of studies and their methodological limitations (Verdoux, 2002). The most convincing pharmaco-epidemiological study to date is one using data on drug exposure prospectively collected on 7866 persons in the Copenhagen Perinatal Cohort (1959–1961), cases of schizophrenia being identified through the Danish Psychiatric Central Register (Sorensen *et al*, 2003). After adjustment for confounding factors, risk of schizophrenia was found to be increased in people exposed to maternal diuretic treatment during the third trimester of pregnancy and was especially marked in individuals also exposed to maternal hypertension.

CONCLUSION

More and more people are exposed to prescribed psychotropic drugs at all stages of the life cycle, from prenatal life to old age. Beyond the societal questions raised by this medical practice, the utilisation and impact of psychotropic drugs have to be further explored at the population level. Pharmaco-epidemiological research conducted independently of drug companies is therefore required to explore crucial public health issues related to psychotropic drug use, such as the medical and economic impact of unjustified extension of use, the identification of infrequent or delayed adverse effects, and the efficiency of new marketed products in naturalistic conditions.

DECLARATION OF INTEREST

H. V. has acted as a consultant to the pharmaceutical companies Bristol–Myers

Squibb, Eli Lilly, Janssen-Cilag, Lundbeck and Sanofi-Synthelabo.

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