Special Article

Pharmacoepidemiology of psychotropic drugs: examples of current research challenges on major public health issues

HÉLÈNE VERDOUX, MARIE TOURNIER, BERNARD BÉGAUD

INSERM U657, University Victor Segalen Bordeaux2, Bordeaux (France)

SUMMARY. **Background** – As a large number of persons are exposed to prescribed psychotropic drugs, their utilisation and impact should be further explored at the population level. **Aims** – To illustrate the interest of pharmacoepidemiological studies of psychotropic drugs by selected examples of major public health issues. **Method** – Selective review of the literature. **Results** – Many questions remain unsolved regarding the behavioural teratogenicity of prenatal exposure to psychotropic drugs, the impact of their increasing use in children, the long-term cognitive consequences of exposure to benzodiazepines, and the risks associated with extension of indications of antipsychotic drugs. **Conclusion** – Pharmacoepidemiological studies need to be further developed owing to the large number of public health questions raised by the extensive and expanding use of psychotropic drugs.
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INTRODUCTION

A large number of persons are exposed to psychotropic drugs worldwide. According to the *European Study of the Epidemiology of Mental disorders* (ESEMED) conducted in 2001-2003, the one-year prevalence of any psychotropic drug use in persons aged 18 years and over was 5.9% in Germany, 7.4% in the Netherlands, 13.2% in Belgium, 13.7% in Italy, 15.5% in Spain, and 21.4% in France (Alonso *et al*., 2004). The Mental Health in the General Population Survey carried out between 1999 and 2003 in 36 785 individuals representative of the French general population found that more than one out of three (36.3%) reported having used at least one psychotropic drug during their life (Grolleau *et al*., 2008).

Owing to this high level of exposure to psychotropic drugs, it is essential from a public health perspective to assess its impact on the health of populations by using pharmacoepidemiological methods. These methods explore the utilisation and impact (benefit and risk) of drugs in real-life conditions at the level of the population actually treated, and not only on the theoretical target population as defined by pre-marketing trials and marketing authorization (Bégaud, 2000; Barbui & Tansella, 2005). A large number of methodological issues are raised by the use of pharmacoepidemiological methods, such as for example quality of information stored in administrative databases. These issues, which are not specific to psychotropic drugs, would deserve a specific review, and we have hence chosen to not discuss them since it is not possible to do so correctly in a few lines.

Owing to the extent of the subject, writing a review on public health questions raised by the use of psychotropic drugs requires a selection of the topics to be discussed. We have chosen to present only selected questions that may be seen as examples of current burning issues. This selection is that of the authors, and other choices could have been made, so it may not reflect that of all researchers involved in this field.

Address for correspondence: Professor H. Verdoux, Hôpital Charles Perrens, 121 rue de la Béchade, 33076 Bordeaux Cedex (France).
Fax: +33-556-563546
E-mail: helene.verdoux@bordeaux2.fr

UTILISATION STUDIES

As examples of issues related to use of psychotropic drugs in real-life conditions, we have chosen to focus on increasing use of psychotropic drugs in children and extension of indications of psychotropic drugs. Considering the huge literature devoted to these points, it was not possible to perform a systematic and exhaustive review of the literature in the format of the present manuscript. Although we attempted to give a fair presentation of the current evidence, our selection of articles may be regarded as partial.

Childhood exposure to psychotropic drugs

There is growing concern regarding the increasing use of psychotropic drugs in children. In 2000, Zito and collaborators published a study showing that prescriptions of psychotropic medications were not exceptional in children aged 2 through 4 years (Zito *et al*., 2000). The most worrying finding was that the prevalence of psychostimulant use was 12.3 per 1000 in this age group in 1995, with a steady increase since 1991. Another study from the same research group (Zito *et al*., 2003) showed that the frequency of psychotropic drug use markedly increased from 1987 to 1996 among youths younger than 20 years, the 1996 prevalence of 6% nearly reaching that found in adults. More recent studies carried out in the US have confirmed this trend (Olfson *et al*., 2002; Martin & Leslie, 2003). Although more marked in the US, it is not restricted to this country (Wong *et al*., 2003). For example, a study carried out in the Netherlands showed that the prevalence of psychostimulant use increased from 1.5 per 1000 in 1995 to 7 per 1000 in 1999 in children younger than 20 years (Schirm *et al*., 2001). An Italian study performed on 1.5 million children and adolescents younger than 18 years showed that the prevalence of any psychotropic drug use was 3 per 1000 during the year 2004 with a marked increasing trend in antidepressant prescription (Clavenna *et al*., 2007). The prevalence of psychotropic drug use in French children younger than 18 years was 3% in 2003, this high frequency being partly due to the inclusion of herbal medicines in the definition of psychotropic drugs (Sevilla-Dedieu & Kovess-Masfety, 2008).

The increasing use of psychotropic drugs in the general population is not restricted to the youngest persons. However, this trend generates specific problems in this age group, in particular regarding the assessment of the benefit/risk ratio of these drugs. Most psychotropic drugs are not approved for use in youths, and their efficacy and efficiency have been poorly assessed in children and adolescents. The risks associated with exposure of a developing person to psychotropic drugs are not clearly documented. These risks may be neurobiological, owing to the potential impact of psychotropic drugs on neurodevelopment. Psychotropic drug use may also impact on the construction of the self and at the interpersonal level, owing to the stigma still associated with the status of psychotropic drug user.

An illustration of this point is the increasing use of antipsychotic drug use in children and adolescents highlighted by recent US pharmacoepidemiological studies (Patel *et al*., 2002; 2005; Cooper *et al*., 2004; 2006; Aparasu & Bhatara, 2005; Olfson *et al*., 2006). As in the adult population, this increase is mainly due to a dramatic rise in the prescription of second-generation antipsychotics (SGAP) (Verdoux *et al*., submitted for publication). This increasing use contrasts with the fact that no SGAPs had been approved for use in persons younger than 18 at the time the surveys were carried out. These drugs are increasingly used in indications such as bipolar disorder, Attention-Deficit Hyperactivity Disorder or conduct disorders, in spite of the lack of evidence regarding their efficacy and efficiency in these indications and in this population (Cooper *et al*., 2004; Olfson *et al*., 2006). Furthermore, children and adolescents may be at greater risk of metabolic disorder compared to adults (Olfson *et al*., 2006).

Hence, there is an urgent need to assess the benefit/risk ratio of psychotropic drugs in children and adolescents, in particular regarding the long-term consequences of exposure of a developing person to these drugs (Greenhill *et al*., 2003a; b).

Extension of indications of psychotropic drugs and disease mongering

Pharmacoepidemiological studies play a key role in identifying extensions of indications of psychotropic drugs and their impact. Extended use may be schematically classified as the widening of labelled indications, off-label prescriptions, and widening of the case definition of the disorder. These three aspects may be illustrated by the example of antipsychotic drugs.

Regarding labelled indications, several SGAPs are now approved for the acute treatment of mania or for maintenance treatment in bipolar disorder. Some recent guidelines recommend use of SGAPs as a first-line option for the maintenance treatment of bipolar disorder

(NICE, 2006; Yatham *et al*., 2006). Hence, these drugs can be used more frequently as first-line treatment for incident bipolar disorders, and persons treated with "classical" mood stabilizers alone (*i.e*. lithium and anticonvulsants) may be switched to SGAPs or treated over longer periods with these drugs. Although it is beyond the scope of this review to debate which drug is or is not a "mood-stabilizer" (Bauer & Mitchner, 2004), the marketing strategy positioning SGAPs at the same level as "classical" mood-stabilizers is clearly aimed at increasing the number and the duration of antipsychotic prescriptions in persons with bipolar disorder.

Off-label use of antipsychotic drugs is not a new phenomenon, as it already existed for first-generation antipsychotics, for example in the maintenance treatment of bipolar disorder (Verdoux *et al*., 1996). However, the introduction of SGAPs has contributed to a dramatic increase of this practice. As mentioned above, there is has been a striking rise in off-label prescriptions of SGAPs in children and adolescents. The same tendency is observed in adult populations, since SGAPs are often prescribed for anxiety disorders (Kaye *et al*., 2003). As emphasized by Linden & Thiels (2001) "from a pharmaco-epidemiological perspective, neuroleptic drugs are anti-neurotic or hypnotic drugs rather than antipsychotic drugs". Off-label prescriptions of SGAPs are also rising in persons suffering from dementia and other organic mental disorders (Dewa *et al*., 2002; Lindesay *et al*., 2003; Trifiro *et al*., 2005; Mirandola *et al*., 2006). A factor explaining this trend may be that SGAPs have narrower labelled indications compared to FGAPs (Veronese *et al*., 2008). The fact that SGAPs are marketed as drugs with few side effects has also probably favoured an extension of the perceived indications for antipsychotic drug use (Cooper *et al*., 2006), since these drugs are no longer considered by prescribers as restricted to persons with severe mental illnesses.

Widening of the case definition of a disorder is a more subtle way to increase the number of persons treated with a drug. Psychiatry is especially vulnerable to the extension of the boundaries of treatable illness or "disease mongering" (Moynihan *et al*., 2002). Although diagnostic criteria such as DSM-IV or ICD-10 have considerably contributed to increasing diagnostic reliability, the validity of the diagnostic categories defined in these international classifications is still uncertain. The boundaries between two disorders, or between a given disorder and normality, and hence between individuals who should or should not be treated, are often arbitrary. Thus, the boundaries distinguishing subjects with and without the disorder can be easily moved to widen the case definition, i.e. persons presenting with subsyndromal disorders being moved to the category of persons in need of treatment. Early intervention in psychosis, which is supposedly aimed at improving the prognosis of persons with incipient psychosis, provides an illustration of the extension of indications by widening the case definition of a disorder (Verdoux & Cougnard, 2003). The underlying postulate is that the threshold distinguishing subjects with and without psychosis (i.e. with and without need of care) should be moved to include subjects with "prodromal psychosis" or "at-risk mental states" (Ricciardi *et al*., 2008). The major limitation of this strategy is that the symptoms listed in the diagnostic criteria of "at-risk mental states" have a poor predictive value, leading to a high number of false-positive tests in the identification of persons at risk for transition to psychosis (Verdoux & Cougnard, 2003; Cougnard *et al*., 2005; Pelosi, 2008). Hence, a deleterious consequence of the implementation of early detection programs may be that a large number of adolescents and young adults are unnecessarily exposed to antipsychotics. There is a striking temporal coincidence between the introduction of SGAPs and the growing interest for early intervention programs (Verdoux & Cougnard, 2003). Pharmaceutical companies might have directly or indirectly contributed to promoting this approach which potentially increases the target population of SGAPs, as they are obviously interested in increasing the size of the treated populations (Moynihan *et al*., 2002; Healy, 2006).

Pharmacoepidemiological studies have already contributed to identifying a large increase in SGAPs prescription in the general population (Ashcroft *et al*., 2002; Dewa *et al*., 2002; Hermann *et al*., 2002; Santamaria *et al*., 2002; Mond *et al*., 2003; Aparasu *et al*., 2005; Rapoport *et al*., 2005; Percudani *et al*., 2006). To date, the only exception to this general trend has been in Italy where prescription of antipsychotics remained stable (Trifiro *et al*., 2005; Mirandola *et al*., 2006). These findings may be due to the fact that the period of interest in the two Italian studies was 1999-2002, whereas SGAPs were refunded only from 2001 in Italy. The next step in pharmacoepidemiological studies will be to identify the impact at the population level of increased exposure to SGAPs, particularly considering the risk of metabolic disturbances induced by these drugs.

Outcome studies

Pharmacoepidemiological studies play a key role in the identification of rare or delayed adverse effects associated with prescription of psychotropic medications,

which cannot be identified in clinical trials. As an illustration of this approach, we have chosen to present two issues, that of behavioural teratogenicity of prenatal exposure to drugs and that of long-term cognitive consequences of benzodiazepine exposure. For these two examples, scarce data are available in the literature. We used a Medline search to identify articles related to these issues using the following key-words (psychotropic/antidepressant/antipsychotic/neuroleptic/lithium/ anticonvulsant/ teratogen*/ behavioural/ behavioral/ prenatal/ pregnancy) for the first issue, and (benzodiazepine/ cognitive/ cognition/ dementia/ long-term/ cohort) for the second issue. Once again, the aim of the present manuscript was not to present a systematic review, hence we cannot exclude that some articles may have been missed.

Behavioural teratogenicity of prenatal exposure to prescribed drugs

The teratogenic risks associated with prenatal exposure to psychotropic drugs are documented by a large body of evidence. The neural tube defects and the cognitive deficits induced by prenatal exposure to anticonvulsants are the most widely acknowledged examples of such adverse effects (Gagliardi & Krishnan, 2003). More recently, studies have suggested that prenatal exposure to selective serotonin-reuptake inhibitors is associated with an increased risk of persistent pulmonary hypertension and cardiac malformations (Chambers *et al*., 2006). In contrast, a limited number of studies have explored the behavioural teratogenicity associated with prenatal exposure to psychotropic drugs (Verdoux, 2004). The hypothesis that prenatal exposure to psychotropic drugs may induce long-term neurobiological disturbances favouring behavioural disturbances is biologically plausible. For example, the deleterious long-term behavioural impact of prenatal exposure to psychoactive substances such as nicotine is well documented (Wakschlag *et al*., 2002). To date, studies have mainly explored the association between prenatal exposure to psychotropic drugs and behavioural disturbances in early childhood (Schou, 1976; Misri *et al*., 2006). While exposed children were not found to be at an increased risk of behavioural problems, some studies reported a possible negative impact of antidepressant exposure on psychomotor development (Casper *et al*., 2003).

This paucity of data is related to the methodological complexity of studies exploring this issue. Although not negligible, the frequency of psychotropic drug use during pregnancy is relatively low in pregnant women (De Las Cuevas et al., 2007; Ramos *et al*., 2007). The prospective collection of drugs should be used to control memory biases (Newport *et al*., 2008). The impact of psychotropic drugs on the risk of behavioural disturbances in children, if any, is likely to be small. Furthermore, it is rather complex to exclude a confounding effect of the psychiatric disorder underlying the prescription of psychotropic drugs in the mother, or that of a common genetic vulnerability explaining both the prescription of a psychotropic drug in the mother and the occurrence of behavioural disturbance in the child. Lastly, the impact of psychotropic drugs may be delayed until late adolescence or adulthood. While there is currently no data clearly demonstrating that prenatal exposure to psychotropic drugs is risky for the behavioural outcome of the child, there is also no data clearly demonstrating that these drugs are free of such adverse effects. Only large prospective cohorts with a prolonged follow-up would provide reassuring data regarding the behavioural teratogenicity of psychotropic drugs.

Regarding non-psychotropic drugs, the most convincing study to date is that performed using data prospectively collected in the Copenhagen Perinatal Cohort and the Danish Psychiatric Central Register to identify subjects suffering from ICD-8 schizophrenia (Sorensen *et al*., 2003). The risk of schizophrenia was increased in subjects exposed to diuretic treatment during the 3rd trimester of pregnancy, especially in subjects also exposed to maternal hypertension. Another study carried out in the same cohort reported that prenatal exposure to analgesics in the second trimester was associated with an increased risk of schizophrenia (Sorensen *et al*., 2004). It has been suggested that prenatal exposure to synthetic estrogens (or xenoestrogens) may increase the risk of adult psychiatric disorder, owing to their potential impact on neurodevelopment. A study comparing the psychiatric outcome of subjects prenatally exposed to diethylstilbestrol with that of their unexposed siblings did not confirm this hypothesis (Verdoux *et al*., 2007). In spite of this reassuring finding, many questions remain unanswered regarding the behavioural consequences of prenatal exposure to drugs with a direct or indirect neurodevelopmental impact, such as other environmental hormones or corticosteroids.

Long-term cognitive consequences of exposure to benzodiazepines

Although a large proportion of persons are chronically exposed to benzodiazepines, few studies have explored the long-term cognitive impact of these drugs. A meta-

analysis of studies carried out in persons recruited in clinical settings for problematic benzodiazepine use showed that former users had poorer performance on most cognitive functions 3 months or more after benzodiazepine withdrawal, particularly with respect to verbal memory (Barker *et al*., 2004). However, these findings are difficult to generalize to the whole population exposed to benzodiazepines, since these studies were conducted on highly selected populations of benzodiazepine users more likely to be exposed to longer duration of use and/or higher dosage of benzodiazepines. In addition, they did not assess the chronological sequence between benzodiazepine exposure and cognitive deficit, which may pre-exist the use of these drugs.

A limited number of prospective studies carried out in general population samples have explored whether chronic exposure to benzodiazepines is associated with an increased risk of incident cognitive decline. As illustrated in a prior review (Verdoux *et al*., 2005), discrepant findings were reported by these studies. One study found a "protective" effect of benzodiazepines on the risk of dementia (Fastbom *et al*., 1998). However, subjects exposed to benzodiazepines only at baseline were not distinguished from those exposed at baseline and at the end of the follow-up. Since benzodiazepines may have been stopped in subjects with incipient dementia, those who were still using benzodiazepines at the end of follow-up were potentially at lower risk of dementia, leading to a spurious association between benzodiazepine use and absence of dementia. Another study reported that subjects using benzodiazepine only at the baseline assessment were at lower risk of cognitive decline (Dealberto *et al*., 1997). Two studies found no association (Hanlon *et al*., 1998; Allard *et al*., 2003). The three other studies reported that benzodiazepine users were at increased risk of cognitive decline, but this risk was restricted to categories of users that differed from one study to another: new users, but not chronic or former users (Dealberto *et al*., 1997); ever and former users, but not current users at the time of diagnosis of dementia (Lagnaoui *et al*., 2002); chronic users, but not occasional users (Paterniti *et al*., 2002). Since this first review, another study carried out in a sample of elderly community-dwelling women in Quebec showed that former use was associated with a 50% increase in the risk of cognitive decline compared to non-use, but the association was not significant (Lagnaoui *et al*., 2009).

These discrepant findings may be explained by the methodological differences regarding the definition of benzodiazepine exposure, duration of follow-up, and measurement and definition of cognitive decline. In all studies, the analyses were adjusted for potential confounding factors, but not all of them explored the impact of psychiatric status, including alcohol use and other psychotropic medications. It is also unknown whether benzodiazepines increase the risk or cognitive decline by interacting with a pre-existing vulnerability.

Hence, pharmacoepidemiological studies suggest that chronic use of benzodiazepines may induce cognitive deficits persisting after withdrawal, but these findings need to be confirmed by further studies. It is particularly necessary to investigate whether there is a dose-response relationship between lifetime exposure to benzodiazepines and the risk of cognitive decline, which would support the hypothesis that a causal relationship may exist between these two characteristics. This issue is of major public importance since a large proportion of elderly subjects are exposed to benzodiazepines in developed countries, and the incidence of cognitive decline is high in this population. Even though benzodiazepine exposure is associated with a small increase in the risk of cognitive decline, a large number of cases of cognitive decline may nevertheless be avoided by restricting benzodiazepine use in this population.

CONCLUSION

The pharmacoepidemiological issues regarding use of psychotropic drugs discussed in the present review have been selected among a long list of major public health concerns. As previously underlined, other choices could have been made. For example, we do not discuss other important points such as the impact of antidepressants on the risk of suicide, the risk of traffic injuries or falls associated with psychotropic drug use, the discrepancies between guidelines and real-life practice, the impact of poor adherence to psychotropic drugs, etc. New pharmacoepidemiological studies are required owing to the large number of questions raised by the extensive and expanding use of psychotropic drugs. It is often a complex task for clinicians in charge of patients to keep in mind the public health questions raised by the use of psychotropic drugs, and to move from assessment of risk and benefits at the individual level to the general population level. Conversely, it is also difficult for public health researchers to be aware of the complexity of the treatments of psychiatric disorders in real-life clinical practice. Hence, as in other fields of psychiatry research, it is of paramount importance to develop a multidisciplinary approach to promote this field of research.

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