Sede Amministrativa: Università degli Studi di Padova
Sede Consorziata: Università di Verona
Dipartimento di: Medicina di Comunità e Sanità Pubblica, Sezione di Farmacologia

SCUOLA DI DOTTORATO DI RICERCA IN: Scienze Farmacologiche
INDIRIZZO: Farmacologia, Tossicologia e Terapia
CICLO: XXIII

Gender differences of ADRs related to psychotropic drug: a survey from Italy, France and Spain

Direttore della Scuola : Ch.mo Prof. Rosa Maria Gaion
Coordinatore d'Indirizzo: Ch.mo Prof. Pietro Palatini
Supervisore :Ch.mo Dott. ssa Anita Conforti

Dottorando: Paola D'Incau

“Knowing is not enough; we must apply.
Willing is not enough; we must do” –Goethe

A mio marito

Preface

Description of research activities conducted within the three years of doctoral school. My research activities within the doctoral school in Pharmacological Sciences addressed in Pharmacology and Therapeutics, began in January 2008 with the study OSIAP (Ordonnances Suspectes Indicateur d'Abus Possible) (http://ec.europa.eu/eahc/projects/database.html). OSIAP program was first developed to investigate and to systematize the identification, the collection and the analysis of suspect prescription forms, in order to validate a reproducible and reliable method for the assessment of the abuse potential of marketed drugs002E Within this program I was involved in the promotion of the study in the Veneto region (Italy), contacting the various local professional associations of pharmacists and organizing an informative meeting in the city of Vicenza (Italy).

Then I followed the community pharmacists participating in the project and I collected their data. I also conducted the research on potential abuse of drugs in Italy following the protocol of the OSIAP European research. During the month of November and December of 2009, during my experience abroad (see below), with the help of Professor Maryse Lapeyre-Mestre (Service de Pharmacologie Clinique Faculté de Médecine de Toulouse, France), head of the OSIAP project, I wrote an article (see Annex 1) on the overall results of project submitted to the European Commission within the Programme "DG Health and Consumer Protection, Public Health area".

At the same time, I started working on the project "Lifestyles: a state of mental and physical health of women" promoted by the Equal Opportunities Commission Region Veneto. This project was developed to investigate, through Veneto community pharmacies the women discomfort and their psychosocial problems that may be related to the use of antidepressants and anxiolytics. I was involved in this project for two years, from January 2008 to October 2010. With Doctor Anita Conforti (Department of Medicine and Public Health Section of Pharmacology University of Verona, Italy), my doctorate tutor, I structured the research protocol and I organized the training sessions with local pharmacists. Later, I was engaged in the collection and elaboration of all data, their elaboration, resulting in writing several articles, abstracts and posters presented at various conferences (see

Annex 2). At the end of the project I collaborated in organizing a meeting open to the citizens to divulgate the results collected.
As a result of the European experience and of the project on women mental health, in the December 2009 a collaboration between the regional centers of pharmacovigilance in the regions of Midi-Pyrénées (France), Castilla-Leon (Spain) and Veneto was promoted. This partnership was established with the primary purpose of investigating the gender difference regarding the adverse drug reactions (ADRs) of psychotropic drugs using the spontaneous reporting system. During my experience in the University of Toulose (France) (November, December 2009 and July 2010), at the "Service de Pharmacologie Clinique Faculté de Médecine CEIP de Toulouse, under the supervision of Professor Maryse Lapeyre-Mestre, I dedicated myself structuring the protocol of research and collecting and processing the data reported in the three pharmacovigilance regional centers about the ADRs reports of antipsychotics, anxiolytics, hypnotics, antidepressant and stimulants reported between 2007 and 2009.

The topic on which I will discuss the doctorate thesis and for which I requested the mention of Doctor Europaeus concerns precisely this new European collaboration.

During these three years of doctoral school, my interest in gender medicine and my experience in projects in the field of pharmacoepidemiology has led me to involve in the following other projects: "Promoting active in pharmacies in the proper use of folic acid: a pilot project"; "Surveillance of adverse events by nurses"; "The pharmacist in the promotion of reporting adverse drug reactions by citizens"; "Use of drugs in neonatology: a procedure Research"; "Medication Errors: an Italian project to reduce adverse events in hospital".
The research activities that I performed during these projects were especially dedicated to the design, dissemination and collection of the data. Only the first and the second mentioned projects have been completed.
The preliminary results of the first project were presented orally during the "*Convegno congiunto Network Italiano Promozione Acido Folico e Coordinamento Nazionale dei Registri delle Malformazioni Congenite"*, 26th November, 2010; Rome, Italy (Paola D'Incau, Massimo Farion, Benedetto Patuzzi, Anita Conforti,

Pietro Carbone, Anna Carreri, Domenica Iacono, Antonella Sanseverino, Domenca Taruscio. Promozione Attiva nelle farmacie al corretto utilizzo dell'acido folico: progetto pilota.)

The main results of the second study were presented in the poster session of the "ISoP Annual Conference", 02-06th November, 2010, Accra, Ghana, and were published as follows: S. Opri, R. Leone, U. Moretti, A. Conforti, P. D'Incau, L. magro, M.Smerghetto and G.P. Velo. Adverse Events and Adverse Drug Reactions in Hospital Observed by Nurses: Prospective Analysis of 4608 Patiens. Drug Saf. 2010:33 (10):922-923.

INDEX

Gender differences of ADRs related to psychotropic drug: a survey from Italy, France and Spain

Abstract

Background: It is well recognized that being female appears to be a risk factor for developing ADRs. A number of studies clearly suggest that ADRs are 50% to 75% more likely in women than in men. It has also been suggested that there is a female preponderance in the number of ADRs experienced with nervous system agents. Results from the European Study of the Epidemiology of Mental disorders (ESEMED) conducted in 2001-2003, highlight that the use of psychotropic drugs was more prevalent among women than men. Anxiolytics, sedatives and hypnotics were more often used, followed by antidepressants and antipsychotics. A female propensity to experience of drug adverse effects may result from “gender” related differences in drug exposure as well as “sex” related differences in drug pharmacokinetics and pharmacodynamics. Nonetheless, the reasons for this increased risk in female patients are not entirely clear, notably whether adverse drug reactions among women reflect an inappropriate use of psychotropic medications.

Objective: The aim of this study is to analyze the difference between women and men of psychotropic drugs ADRs reported in the regional pharmacovigilance centre of Midi-Pyrénées (France), Veneto (Italy) and Castilla-Leon (Spain) using spontaneously reported reactions. Specifically the spontaneous reports of ADRs studied regarded antipsychotics, anxiolytics, hypnotics, antidepressant and stimulants that were reported between 2007 and 2009.

Methods: Within the French, Italian and Spanish Pharmacovigilance System databases, the case/non-case method was used to measure the association with the exposure of psychotropic medications of interest and gender. Cases were the reports corresponding to the ADRs related at least to one type of psychotropic drugs of interest and the non-cases are all reports of ADRs other than that being

studied. The association was estimated by calculating a reporting odds ratio (ROR) with its 95% confidence interval (CI).

Results: A total of 967 patients were included in the study, 592 (61%) were female and 375 (39%) were male (p< 0,001). Mean age of the study population was 51 years (range 08-97 years). The association between the use of psychotropic medications of interest and gender was statistically significant for women taking antidepressants (ROR crude =1.67; 95% CI 1,35-2,06; ROR stratified for seriousness =1,71; 95% CI 1,39-2,11; ROR stratified for age = 1,53; 95% CI 1,24-1,90; ROR stratified for age and seriousness =1.54; 95% CI 1,25-1,90) [all p < 0,001].
Analyzing all reports of ADRs reported, the most involved drugs were risperidone (14 % of the total N05A drugs), alprazolam (14 % of the total N05B drugs), zolpidem (32% of the total N05C drugs), paroxetine (16 % of the total N06A drugs) and methylphenidate (39% of the total N06B drugs), while the most associated with sex, in particular with female sex, were lithium carbonate (p<0.05) and prazepam (p<0.05), and with male sex were clozapine (p<0.05) and sertraline (p<0.05).
The most frequent type of ADRs reported in all women reports were classified as “Central & peripherical nervous system disorders” (24%) and “Psychiatric disorders” (18%), while in all men reports were “Body as a whole - general disorders” (14%) and “Resistance mechanism disorders” (13%).

Conclusions: The present study which investigated the role of gender in ADRs reported to a regional French, Italian and Spain Pharmacovigilance centres indicates that female sex is a risk factor for the development of ADRs related to psychotropic drugs especially to antidepressants.
Further research should be performed to investigate the sex-specific drug safety of psychtropic use, taking into account potential risk factors, not only in relation to pharmacogenetics, pharmacokinetics and pharmacodynamics, but also in psychological, social, economic, political and cultural aspects.

Riassunto

Introduzione. È ormai ampiamente riconosciuto come le differenze tra donne e uomini possano influire sulla risposta al trattamento farmacologico e sulla sicurezza dell'impiego dei farmaci nelle due diverse popolazioni. Il genere femminile sembra essere un fattore di rischio per la manifestazione delle reazioni avverse ai farmaci (ADR): le donne hanno una probabilità del 50-75% superiore rispetto agli uomini di manifestare un' ADR. I farmaci psicotropi rappresentano una delle classi maggiormente coinvolte nella manifestazione degli eventi avversi. Dai risultati di uno studio europeo ESEMED (Epidemiologia dei Disturbi Mentali) emerge come Francia, Italia e Spagna rappresentino i paesi in cui sono state rilevate le più alte percentuali di utilizzo di farmaci psicotropi. Gli ansiolitici, i sedativi e gli ipnotici sono stati rilevati in questo studio come gli psicofarmaci più frequentemente utilizzati, seguiti dagli antidepressivi ed ansiolitici. La propensione delle donne alla segnalazione, nonché le differenze delle donne rispetto agli uomini nella farmacocinetica e farmacodinamica, l'età, il numero dei farmaci prescritti alle donne possono chiaramente influenzare l'entità della segnalazione. Nonostante queste evidenze, le ragioni di questo aumento del rischio in pazienti di sesso femminile non sono del tutto chiare, in particolare se le reazioni avverse al farmaco tra le donne riflettono un uso improprio dei farmaci psicotropi.

Obiettivi. Lo scopo principale dello studio è stato quello di indagare le differenze tra la popolazione maschile e quella femminile riguardo alla comparsa di ADRs da farmaci psicotropi, rilevate nel centro di farmacovigilanza della regione del Midi-Pyrénées (Francia), del Veneto (Italia) e della Castilla y Leòn (Spagna), utilizzando dati provenienti dalla segnalazione spontanea. Nello specifico, sono stati rilevati tutti i report di segnalazione delle ADRs relative alle seguenti classi di psicofarmaci: antipsicotici, ansiolitici, ipnotici, antidepressivi e stimolanti; riportate tra il 1 gennaio 2007 e il 31 dicembre 2009.

Metodo. Le ADRs sono state classificate secondo il sesso, la gravità, la tipologia della reazione, l'esito, i farmaci sospetti ed i farmaci concomitanti assunti. La distribuzione per sesso è stata analizzata con il metodo caso-non caso (report

associati alle 5 categorie di psicofarmaci in studio e report associati a tutti gli altri farmaci) calcolando il reporting odds ratio (ROR) crudo e aggiustato su tutte le variabili, e considerando un intervallo di confidenza del 95% (IC 95%).

Risultati. Un totale di 967 pazienti sono stati inclusi nello studio, 592 (61%) era di sesso femminile e 375 (39%) era di sesso maschile (p <0,001). L'età media della popolazione in studio era di 51 anni (range 08-97 anni). L'associazione tra l'uso di farmaci psicotropi di interesse e il genere è stata rilevata statisticamente significativa per le donne che assumevano antidepressivi (ROR grezzo = 1,67, IC 95% 1,35-2,06; ROR stratificato per gravità = 1,71, IC 95% 1,39-2,11; ROR stratificato per età = 1,53, IC 95% 1,24-1,90; ROR stratificato per età e gravità = 1.54, IC 95% 1,25-1,90) [tutte le p <0.001].
Dall'analisi di tutti i report di ADRs segnalati, i farmaci maggiormente coinvolti sono stati: il risperidone (il 14% di tutti i farmaci appartenenti alla classe ATC N05A), l' alprazolam (il 14% degli N05B), il zolpidem (il 32% degli N05C), la paroxetina (il 16% degli N06A) e il metilfenidato (il 39% degli N06B). I farmaci, invece, maggiormente associati al sesso, in particolare al sesso femminile, sono stati il carbonato di litio (p <0,05) e il prazepam (p <0,05), e al sesso maschile sono stati la clozapina (p <0,05) e la sertralina (p <0,05).
La tipologia di ADR più frequentemente riportata dalle donne riguardava " disturbi del sistema nervoso centrale" (24%) e "disturbi psichiatrici" (18%), mentre negli uomini "disturbi generali "(14%) e" disturbi nei meccanismi di resistenza "(13%).

Conclusioni. Dal presente studio è possibile osservare come il sesso femminile rappresenti un fattore di rischio per lo sviluppo di reazioni avverse correlate a farmaci psicotropi, soprattutto in riferimento agli antidepressivi.
Ulteriori ricerche dovrebbero essere effettuate per valutare la sicurezza dell'uso di farmaci psicotropi in funzione del sesso, tenendo conto dei potenziali fattori di rischio, non solo relativi alla farmacogenetica, farmacocinetica e farmacodinamica, ma anche ad aspetti psicologici, sociali, economici, politici e culturali.

Introduction

1. Adverse drug reactions

Adverse drug reactions (ADRs) were defined according to the World Health Organization's adverse reaction terminology[1] revised by Edwards and Aronson as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product".[2]

ADRs represent a major public health problem in terms of hospitalization, morbidity and cost, as reported by many studies, conducted in hospitals, emergency departments and ambulatory care settings.[3] The spontaneous reporting systems of adverse drug reactions has contributed significantly to the successful of pharmacovigilance, the post marketing surveillance system of drugs addressed to analyzing and managing the risks associated with drugs once they are available for the use of the general population. [4,5] Spontaneous reporting has the great advantage of covering a large number of patients and wide range of drugs and of being a relatively cost-effective method of monitoring drug safety. In spite of these benefits, under-reporting is a major draw-back of spontaneous reporting. It is estimated that only 6–10% of all ADRs are reported.[6,7] A part from these limitations, spontaneous reporting of adverse drug reactions remains the only surveillance system capable of routinely monitoring the safety of drugs.[8] This approach allows not only identification of iatrogenic risk or iatrogenic syndromes but may also permit comparison of ADR characteristics between groups of patients.[8] It is estimated that approximately 75% of ADRs are dose related and approximately 25% of ADRs are idiosyncratic such as hypersensitivity and allergic.[9] Lazarou and colleagues suggested that 4,7% of hospital admission were related to serious ADR, with an overall fatality rate of 0,32%.[10] By contrast, data on ADRs occurring after hospital admissions suggested that 10.9% of patients suffer ADRs of all severities as in-patients.[11] In a large-scale prospective study on hospital in-patients, Davies et al. showed that out of the 3695 patient episodes assessed for ADRs, 545 (14,7%, 95% CI 13,6–15,9%) experienced one or more ADRs.[11] The patients experiencing ADRs were more likely older, female, taking a

larger number of medicines, and had a longer length of hospitalization than those without ADRs.[11] Half of ADRs were definitely or possibly avoidable. [6] It has been estimated that 83% of ADRs in males and 93% in females are due to dose related effects.[12] A large number of studies has suggested that a female preponderance in the overall frequency of ADRs, women have a 50% to 75% higher risk of developing ADRs than men.[13,14] It has also been suggested that there is a female preponderance in the number of ADRs experienced with general antiinfectives (60,4%), nervous system agents (21,5%), and musculoskeletal agents (3,7%).[14] Females present more commonly with gastrointestinal and coetaneous allergic reactions.[12] Skin-related reactions, in particular, accounted for 49,0% of all reported adverse drug reactions.[14] More than 1 agent was reported to be responsible for the ADRs in 50% of the female patients, compared with 33,1% of all male patients.[15]

2. Adverse drug reactions and women

How might gender modulate the emergence and reporting of ADRs? The answer is rather complex and up to now remains a matter of debate.[15]
On the one hand, the “sex” differences refers to biological and genetic characteristics of men and women have been suspected of being responsible factors.[16] Women and men differ in physical (body-water space, muscle mass, organ blood flow, organ function) and physiological aspects (menopause, pregnancy and menstruation) as well as regarding pharmacodynamics and pharmacokinetics (bioavailability, distribution, metabolism, excretion).[17]
On the other hand, the “gender” differences refers to a set of economic, social, political and cultural attributes and opportunities associated with being male and female, may be decisive for the occurrence of ADRs. [16]

2.1 “Sex” differences in the occurrence of ADRs

Differences between the sexes pervade all clinical experience in medicine: clinical manifestations, course, and therapy of disease. [18] The direct mechanisms of most phenomena involved in sexual dimorphism have not yet been identified. Yet, it is highly likely that these mechanisms will be elucidated through study of systemic or

local expressions of the fundamental differences between the sexes in the genetic and endocrine controls. [18]

For instance, the influence of androgens and estrogens to the DNA transcription has developmental and potentially behavioral consequences that could not be predicted on the basis of circulating hormone levels. This may be particularly important in the brain, with respect to sexual behavior, sexual identity, partner choice, and other sex-related events. [18]

The biologic and molecular differences between men and women reveal in the amount of drug available for therapeutic action after administration (pharmacokinetics) and in the variability in therapeutic properties and adverse effects of medications (pharmacodynamics).[19,20,21]

2.1.1. Pharmacokinetics

Sex-based differences in the four major determinants of pharmacokinetic variability – bioavailability, distribution, metabolism and elimination – are theorized to stem from variations between the sexes in factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, CYP activity, drug transporter function and clearance activity.[15,19]

Box a/b summarizes the various factors that contribute to each pharmacokinetic variable and sex differences that have been identified for these factors.[15,19]

Box 1a: Sex differences in pharmacokinetic parameters [15,19]

	Components	**Sex-based differences**
Bioavailability	Passive component: gastrointestinal tract physiology.	Gastric emptying time is slower in females than males, mainly secondary to the effects of estrogen.
	Active component: extrusion by drug transporters, such as intestinal p-gp (-glycoprotein).	Intestinal p-gp levels do not consistently seem to vary by sex.
	Gut metabolism: gut enzymes, such as alcohol dehydrogenase and intestinal CYP3A4.	Gastric levels of alcohol dehydrogenase are higher in males than females; intestinal CYP3A4 levels do not consistently vary by sex.

Note: enterocytes also express significant levels of isoenzymes of cytochrome P450 3A (CYP3A), which contribute significantly to the first-pass metabolism of some orally administered drugs;

Box 1: Sex differences in pharmacokinetic parameters [15,19]		
Distribution	Body composition: body mass index, percent body fat, plasma lower volume, and organ blood flow.	Women have lower body weights and BMI than men; women have a higher proportion of body fat than men; plasma volume is greater in men than women, although volume varies throughout the menstrual cycle and during pregnancy; organ blood flow is greater in women than men.
	Protein binding: extent of tissue and protein binding of the drug.	Albumin concentrations do not seem to consistently vary by sex, but endogenous estrogens decrease levels of AAG in the plasma, so women have lower concentrations of AAG than men. Exogenous estrogens increase levels of the serum-binding globulins (such as sex-hormone binding globulins, corticosteroid-binding globulin, and thyroxine-binding globulin). During pregnancy, the concentration of albumin, along with other plasma proteins, decreases. However, the effects of pregnancy on the concentration of AAG is under debate:
Metabolism	Hepatic enzymes: Phase I metabolism reactions in the liver include oxidation, reduction, and hydrolysis and are mediated through the cytochrome P450 system.	Data on varying levels of CYP expression and activity using in vitro systems exist, but the majority of studies that examine CYP (mainly CYP3A4) substrates for differences in pharmacokinetic parameters in men and women are inconsistent; general trend toward higher rates of metabolism for CYP3A4 substrates in women versus men. CYP2D6 and CYP2E1 have more activity in men than in women. CYP2C9 and CYP2C19 have the same activities in men and in women.
	Hepatic transporters: hepatic p-gp or MDR1.	Men seem to have higher hepatic p-gp levels than women, with higher rates of drug clearance in women versus men for drugs that are substrates of p-gp.
	Phase II metabolism: glucuronidation, sulfation, acetylation or methylation of the parent drug or its phase I metabolite to generate polar conjugates for renal excretion.	Although most evidence indicates the existence of substantial racial variations in prevalence of specific genotypes, some findings support the occurrence of sex differences in reactions involved in phase II metabolism: thiopurine methyl transferase, glucuronidation, dihydropyrimidine dehydrogenase, UDP-gluronosyl transferase, catechol-O-methyl transferase have more activity in men, while N-acetyltransferase has no sex differences in activity.
Excretion	Renal clearance: renal excretion is dependent on filtration, secretion, and reabsorption.	Renal clearance of drugs that are not actively secreted or reabsorbed is dependent on GFR, which is directly proportional to weight; sex differences for these drugs are attributable to weight differences. Drugs that are actively secreted by the kidney may show sex differences in excretion.

Note: body mass index (BMI); systemalpha-1 acid glycoprotein (AAG).

2.1.2. Pharmacodynamics.

Pharmacodynamic disparities in drug response based on sex have not been studied as extensively as pharmacokinetic differences, partially because pharmacologic effects can be difficult to quantify.

Even though pharmacokinetic gender effects are often of higher magnitude, pharmacodynamic variability among individuals is most often larger than pharmacokinetic variability, and thus is the determinant of interindividual differences in therapeutic response. [21]

Sex-related effects on pharmacodynamics are distinguished from differences in pharmacokinetics by demonstrating that the same plasma concentration of a drug in the two sexes does not yield the same pharmacologic outcome. [19]

2.2. "Gender" differences in the occurrence of ADRs

It is well known that women and men differ in life expectancy – a pattern which can be observed only with few exceptions worldwide. Researchers have shown that women generally live longer than men, despite healthy life expectancy is greater in men than in women.[22,23] In Europe the life expectancy for men was estimated approximately for men 74 years, while for women 80 years (source EUROSTAT 2009). An inevitable consequence of the fact that women live longer appears to be the greater diminution of their physiological functions which leads them to become more fragile and subject to various diseases.[24] Women, in fact, seem to report more illness and use more health care services and medication than men.[23]

Research on gender differences in physical health suggests that women are more likely to have chronic debilitating conditions, such as arthritis and migraines, whereas men are more likely to have life threatening conditions, such as cardiovascular disease and cerebrovascular disease.[25] The evidence does suggest that women visit physicians more than men do and use other diagnostic services more than men.[23] This is due partly because of a series of physiological events such as menstruation, pregnancy, breastfeeding and menopause, which may lead the women to consult an health professionals.[22] At the same time, women are more likely to be given a prescription when visiting a physician: their expectation as well as the physician characteristics (graduation and sex) may

influence whether a prescription is given. [23] The pejorative attitudes toward female patients in medical advertisements have been documented.[26]
Several studies have demonstrated female gender is a predictor of lower status, lower participation in decision-making and lower pay.[27] Women are also disadvantaged as a result of the multiple roles they perform in society - worker, mother, partner, etc. - and, at the same time, of the expectations that our society associate with the general gender roles.[28] Women are more likely to have experienced poverty and discrimination and are more often victims of physical and sexual abuse. Women more often than men complain with housing problems, loss of a confidant, close relationship problems, and illness of individuals in the broader sphere of relatives and friends as stressful life events.[29] To implement the discomfort arising from this social role, women visit the general practitioner more easily than men, while men find a solution more frequent outside of the health system (eg alcohol abuse). [22]
The reflection regarding the reasons for “gender” differences between men and women, may be also read in light of the so-called "gender bias".[16] This type of bias most often refers to the fact that (1) medicine was accused of being “gender-blind” by not taking gender under consideration whenever relevant (medication studies result are inadequately tested in female humans and/or animals; (2) it is said that medicine is “male-biased” or “androcentric” because the body of knowledge on health and illness is predominantly about men and their health; (3) the pursuit for masculinity or femininity may lead to actual gender differences in health problems; (4) the gender inequality: no equal opportunities, in the allocation of resources and benefits, or in access to services (WHO 2002).[15,16,18,23]

3. Psychotropic drugs and women

It has long been recognized that a large number of people are exposed to psychotropic drugs worldwide.[30] Results from 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. [31] From this study emerges that the use was more prevalent among women than men, and in older rather than in younger age

groups.[32] Anxiolytics, sedatives and hypnotics were more often used, followed by antidepressants and antipsychotics. [32] It is well known that, the prevalence of mental health conditions that are typical indications for these medicines is usually higher among women.[31-33]

What is the relation of reported differences in psychotropic drug use between men and women?

The debate can be analyzed in the light of the “sex” and the “gender” perspective.

3.1 “Sex” perspective

As previously reported, the biological factors, such as endocrine imbalances, menstrual cycle-related hormonal fluctuations, reproductive events, and menopause, play important roles in the etiology of mental and behavioral changes in women.[18,33] Psychiatric symptoms can arise from a number of illness common in women, such as neurologic, autoimmune, endocrine and hematologic disorders. For example, the most common endocrine disorder in women is hypothyroidism, which can often leads to manifest depression symptoms. [33]

After puberty, women have the highest rates of generalized anxiety, major depression, and mixed anxiety –depression disorders, all of which are associated with unexplained physical symptoms and disability. Examples of psychiatric disorders more common in women and in men include the following (Box 2):

Box 2: psychiatric disorders and conditions[33]

Psychiatric disorders more common in women than in men:	**Psychiatric disorders more common in men than in women:**
• mood disorders • anxiety disorders, • eating disorders, • sleep disorders, • personality disorders, • somatoform disorders, • dissociative disorders, • obsessive-compulsive spectrum disorders, impulsive-control disorders, • late-onset schizophrenia, • dementia and Alzheimer’s type.	• early-onset developmental and neurologic disorders, • elimination disorders, • impulsive-control disorders, • sexual and gender identity disorders, • bipolar disorders, • substance-related disorders, • some personality disorders.
Bipolar I disorder, obsessive-compulsive disorder, hypochondriacs, and body dimorphic disorder occur equally in men and in women.	

3.1.1 Pharmacokinetics

Gender-specific differences have been identified for numerous molecular and physiological factors affecting the pharmacokinetics of psychotropic agents, and even more aspects might be discovered by ongoing research on drug-metabolising enzymes and transporters.[15,21] Response rates to pharmacologic treatment used in mood disorders have shown sex differences – for example, a higher response rate to imipramine in men; a more rapid response to acute tricyclic antidepressant (TCA) treatment with sustained clinical response in men. Boxes 3a and b show some examples of psychotropic drugs difference in pharmacokinetic variables.[9,15,20]

Box 3 a : Sex differences in pharmacokinetic parameters of some psychotropic medications [9,15,20]

	Psychotropic medications
Bioavailability	• Antipsychotics required 1.5 to 2-fold higher dose in men compared with women. • Midazolam have demonstrated higher bioavailability in women.
Distribution	• Sex related differences in blood concentrations have not been found in the risperidone, quetiapine and ziprasidone therapy, when the data is corrected for body wheight. • Major volume of distribution for diazepam in women, responsible for the longer duration of effects induced by the prolonged elimination time.

Box 3 b : Sex differences in pharmacokinetic parameters of some psychotropic medications [9,15,20]

	Psychotropic medications
Metabolism	• CYP1A2, 2C19, 2D6 and 3A4 are the most important hepatic enzymes for antipsychotic and antidepressants drugs. • Lower enzyme activity of CYP1A2 has been shown in women. Dose related plasma concentrations of olanzapine were significantly higher in women. • The antipsychotic agents thiothixene, olanzapine and clozapine, all CYP1A2 substrates, also exhibit a significant higher clearance in men than in women. • Mirtazapine, sertraline and desipramine, CYP2D6 and CYP3A substrates, have been reported to exhibit faster clearance in men. • CYP2C19 represents the major catabolic pathway for therapeutic agents such as citalopram. • Smoking induces CYP1A2 resulting in significantly lower blood concentrations of olanzapine and clozapine in smokers.
	• Such variations on the phase II metabolism might be of significant importance in neurotransmitter metabolism that influences the effect of psychopharmacological agents.
Excretion	• The lower glomerural filtration rate in women results in 40-50% higher amisulpride plasma levels

3.1.2 Pharmacodynamics.

Many psychotropic medications also appear to exhibit sex-mediated differences in pharmacodynamics. Women show greater improvement in psychotic symptoms and more severe adverse side effects with typical antipsychotic agents than do men. Therapeutically relevant gender effects in pharmacodynamics have clearly been identified, for example with regard to drug induced QTc prolongation, effect of antipsychotic drugs.[21,24] Furthermore, men and women appear to show differential effects to various antidepressant agents, although more work is needed to study as to whether these differences are mediated through pharmacokinetic or pharmacodynamic.

Some examples of pharmacodynamic differences between men and women of CNS drugs are summarized in the following box (Box 4 a and b).[9,15,20]

Box 4 a: Sex differences in pharmacodynamic parameters [9,15,20]

Sex-based differences	**Reflection on psychotropic medications**
Women have been reported to exhibit significantly higher dopamine D2-like receptor binding than men in the frontal cortex.	Clozapine and fluphenazine resulted equally effective in increasing basal ganglia and decreasing cingulated metabolism in women but not in men
Women displayed higher [18F]-fluorodopa uptake than men into striatum, thus suggesting that female sex hormones enhance presynaptic dopamine turnover.	In general, females are more sensitive to cocaine and methylphenidate as well as to other psychostimulant drugs.

Box 4 b: Sex differences in pharmacodynamic parameters [9,15,20]

Sex-based differences	**Reflection on psychotropic medications**
Women could have a more susceptible serotonergic system compared with men, and therefore could respond disproportionately to extraneous factors, including medications.	Fluoxetine treatment raises serum tryptophan about 83% and 32% in women and in men, respectively, and l-triiodothyronine augmentation hastens the onset of tricyclic antidepressant (TCA) response to a greater extent in women than in men.
The differences between men and women in the dependency-producing properties might be ascribed to different brain levels of neuroactive steroids, which have been reported to affect GABAA receptors in a sex-specific manner.	The majority of patients who are prescribed benzodiazepines and are treated for benzodiazepine dependency are women.

3.2 “Gender” perspective

In the last century the medical views located most women’s problems in their reproductive organs.[26] Modern medicine has moved far beyond this reproductive explanation of female illness to its 20th century equivalent: the weak central nervous system or the psychologically inadequate woman. Contemporary thought holds that changes in women’s role in society have resulted in increase stress, leading to increases in the rates of psychotropic or psychosomatic illness, hence resulting in increased use of psychotropic drugs. [26]

The effect of exposure to stressful life events may cause distress reactions that trigger psychological, biological, behavioral, and attentional mechanisms that precede the onset of depressive and anxiety disorders and, as a consequence, may lead to high use of psychotropic drugs. [34-37] Research on gender differences in mental health has clearly established that women have higher rates of so-called “internalizing” disorders, including mood and anxiety disorders, while men have higher rates of “externalizing” disorders, including , autism, learning disabilities, attention-deficit and substance use disorders.[23,34,35] Available data on men’s and women’s awareness of discomfort indicate that women consistently report more symptoms of both physical and emotional discomfort then men.[26,35] Whether these differences reflect a greater sensitivity of women to their emotional and bodily reactions, that is a greater ability to feel or express discomfort remains a moot point.[39]

Analyzing the reasons for women’s higher rate of psychotropic use, it has been to consider that:

1) women consult with physicians more often and as a result are at higher risk by virtue of the fact that their opportunities for receiving a prescription have been increased;[39]

2) women are more familiar with drugs and their effects, are more likely to ask for these drugs, are better at convincing physicians of their need for drugs, and/or men are better at refusing drug prescriptions;[39]

3) physicians are overresponding to women's expressed emotions and overprescribing;[39]

4) primary care providers a crucial role in the management of psychiatric disorders.[32]

ESEMeD survey shows that the 10% of individuals use a psychotropic drug in the previous 12 months without a psychiatric diagnosis. As Harman reported,[40] the increasing of mental health treatment might be due to change in locus of treatment from the specialist sector to the primary care sector, the availability of SSRIs and the cost containment pressures. Women with affective disorders may consult more often a family physician, which may make access easier. [23,33]. However, women do not receive prescriptions for more psychotropics of all types; they receive more prescriptions than men for anxiolytics and for antidepressants, but not for hypnotics or barbiturates or for antipsychotics.[16] Women were also more likely than men to receive diagnoses of depression and be reported to complain of fatigue and anxiety. [16] Men were more likely to receive a diagnosis of alcoholism or alcohol abuse, although these are often problems not interpret as signs of mental disorder that can be alleviated by psychotropic medication. [16] The "gender role ideology" may leads doctor to perceive women's health problems with social or psychological origins, thus undermedicalisation men's mental health.[17]

4. Sex differences in psychotropic adverse drug reactions.

The correlation of the large number of people reporting mental health problems and the consequent consumption of psychotropic drugs necessarily leads to reflect on the occurrence of adverse drug reactions. Sex differences observed in the adverse effects associated with psychotropic drugs have not been reported consistently in the literature.

The most frequent side effects associated with gender, and in particular with female sex, reported in a recent review are: weight gain and metabolic syndrome induced by antipsychotics, symptoms of sexual dysfunction caused by antidepressants and antipsychotics, cardiac arrhythmic side effects associated with antipsychotic drugs.[9]

Other major adverse effects of psychotropic drugs are summarized in the Box 5 a,b,c.

Although the incidence of the occurrence of side effects following a psychopharmacologic therapy appears "sex"-related in pharmacokinetics and pharmacodynamics, "gender" differences in efficacy and toxicity should also

consider in the ADRs evaluation. Sociodemographic characteristics and lifestyle factors as well as biological and genetics determinants play a significant role in the onset of adverse drug reactions.

Box 5 a: psychotropic drug reactions; focus on women [9, 40,41]

Psychotropic drugs	Common adverse drug reactions	Major side effects reported in women
Antipsychotics (general)	Drowsiness, dizziness when changing positions, blurred vision, rapid heartbeat, sensitivity to the sun, skin rashes menstrual problems for women.	• Metabolic syndrome caused by antipsychotics drugs is more prevalent in women than in men. • Stronger metabolic changes, cardiovascular disease and sudden cardiac death are reported in men than in women. • Prolactin elevations are more pronounced and more frequent in women respect in men. • The menstrual irregularities and the osteoporosis are the consequence of hypogonadism and the reduction of bone mineral density induced by the hyperprolactinemia. • The prolongation of QT interval which increases the risk of life-threatening torsade de pointes and sudden death has been observed in women compared with men. • Ventricular arrhythmia associated with QTc interval is higher frequent in women.
Typical antipsychotics (e.g. chlorpromazine, haloperidol, perphenazine, fluphenazine).	Dry mouth, muscle stiffness, muscle cramping, tremors, extrapyramidal side effects (EPS: a cluster of symptoms consisting of akathisia, parkinsonism, dystonias), tardive dyskinesia (TD: no control of the muscle movements).	• Tardive dyskinesia is higher in elderly men and in post-menopausal women, but there is no clear –cut sex difference.
Atypical antipsychotics (e.g. amisulpride, aripiprazole, clotiapine, clozapine)	Weight gain, type II diabetes mellitus, hyperlipidemia, QTc interval prolongation, myocarditis, sexual side effects, extrapyramidal side effects and cataract.	• Weight gain in women: low pretreatment BMI, young age and female sex have been shown to be an important predictor for body weight gain in patients with a atypical antipsychotics. • The lower risk for TD observed in the atypical antipsychotics might be reduced at higher doses used. Thus, there might be a higher risk for women due to differences in drug exposure when administering the same dosages as in men.

Box 5 b: psychotropic drug reactions; focus on women[9, 40,41]		
Psychotropic drugs	**Common adverse drug reactions**	**Major side effects reported in women**
Mood stabilizers: lithium, anticonvulsivants (e.g. valproic acid, lamotrigine, carbamazepine), atypical antipsychotics (e.g. olanzapine aripiprazole, risperidone, clozapine)	**Lithium**: nausea, vomiting, and diarrhea, trembling, increased thirst and increased need to urinate, weight gain in the first few months of use, drowsiness, a metallic taste in the mouth, abnormalities in kidney function, abnormalities in thyroid function.	• A higher prevalence of hypothyroidis before the onset of lithium treatment has been described in women versus men. • Weight gain is very common and might be of greater concern of female patients compared with men.
	Anticonvulsivants **Valproic acid**: nausea, diarrhea, abdominal cramps, sedation, tremor, weight gain and rash. **Lamotrigine**: headaches, sleepiness, weight gain, Stevens-Johnson syndrome. **Carbamazepine**: nausea, dizziness, sedation, headache, dry mouth, constipation and rash	• Valproic acid: plasma leptin, high-density lipoprotein, the frequency of carbohydrate craving symptoms and disturbances in glucose homeostasis and lipid metabolism were significantly higher in women versus men. • Valproic acid: polycystic ovary syndrome (PCOS) has been reported in the treatment for epilepsy. • Carbamazepina and alproic acid: hematological side effects (leucopenia and thrombocytopenia) occur more frequent in women. • Skin side effects occur more frequent in women than in men.
Antidepressants: the most commonly types of drugs associated with this term are: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) .	**MAOIs**: hepatitis, heart attack, stroke, seizures and serotonin syndrome. **TCAs**: mouth, blurred vision, drowsiness, dizziness, tremors, sexual problems, skin rash, and weight gain or loss. **SSRIs**: nausea, diarrhea, agitation, headaches, sexual side effects, serotonin syndrome, suicidal rates in children and adolescents **SNRIs**: because the SNRIs and SSRIs both act similarly to elevate serotonin levels, they subsequently share many of the same side effects, though to varying degrees. The most common include loss of appetite, weight, and sleep.	• Sexual dysfunction vary across antidepressants with highest rates occurring for SSRIs and venlafaxine, mirtazapine and moclobemide. • Sexual dysfunction may be higher in men, whereas women tend to sexual desire as a consequence of suffering depression.

Box 5 c: psychotropic drug reactions; focus on women[9, 40,41]		
Psychotropic drugs	**Common adverse drug reactions**	**Major side effects reported in women**
Anxiolytics & hypnotics (benzodiazepines: e.g. diazepam, nitrazepam, zolpidem chlordiazepoxide, alprazolam).	Sedating and muscle-relaxing action (drowsiness, dizziness and decreased alertness and concentration), impairment of driving skills, decreased libido and erection problems, depression and disinhibition, hypotension and suppressed breathing. The long-term adverse effects of benzodiazepines include a general deterioration in physical and mental health and tend to increase with time. Withdrawal syndrome represents the main problem of the chronic use of benzodiazepines.	ADRs differences in women and in men were no reported in the review (See the Box 3)
Stimulants for treatment of attention-deficit hyperactivity disorder (ADHD) (e.g. methylphenidate, dexmethylphenidate, dextroamphetamine & levoamphetamine, modafinil).	Decreased appetite, sleep problems, stomachaches and headaches.	ADRs differences in women and in men were no reported in the review (See the Box 3)

The aim of the current work.

On the basis of these assumptions, the aim of this study is to analyze the difference between women and men of psychotropic drugs ADRs reported in a regional pharmacovigilance centre of Midi-Pyrénées (France), Veneto (Italy) and Castilla-Leon (Spain) using spontaneously reported reactions. Specifically the spontaneous reports of ADRs studied regarded antipsychotics, anxiolytics, hypnotics, antidepressant and stimulants that were reported between 2007 and 2009.

Methods

1. Data collection and analysis

The data were obtained from the French, the Italian and the Spanish Pharmacovigilance System databases which include all of the voluntary submitted reports of ADRs reported to the Midi-Pyrénées (France), Veneto (Italy) and Castilla-Leon (Spain) Regional Pharmacovigilance Centres, since 1985, 1987 and 1982 respectively.[43] In France, spontaneous reporting from all prescribers (medical doctors, dentists or midwifes) and all pharmacists is compulsory since 1995 for all ADRs defined as 'serious' or 'unexpected'.[43].In Italy, spontaneous reporting from doctors and pharmacists has been mandatory since 1987 while for nurses since 2003. The health practitioners have to send all suspected ADRs to the Local Health Districts (around 200 in whole country), that forward reports to Ministry of Health.[44] Spain, information comes mainly from spontaneous reporting compulsory for health professionals since 1990.[43]

In all three regional pharmacovigilance systems, reports are included in the database after evaluation of causality and seriousness level. [4,43,44]

We analysed the spontaneous reports of antipsychotics, hypnotics, anxiolytics, antidepressants and stimulants reported as suspected drugs between 1 January 2007 and 31 December 2009 in terms of:

1. **Sex**: female and male.

2. Type of **Anatomical Therapeutic Chemical Classification System** (ATC) system for Human Medicine. [45] The psychotropic drugs considered in this study were classified according to the 4th level of ATC (Box 6). This system classifies active substances into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Drugs are classified in groups at five different levels: the first level is the anatomical group and consists of 1 letter; the second level of the code is based on the therapeutic main group and consists of 2 digits; the 3rd and 4th

levels are chemical/pharmacological/therapeutic subgroups and the 5th level is the chemical substance.

Box 6. The N ATC code and its therapeutic main groups[45]

II level	III level	IV level
N01	Anesthetics	
N02	Analgesics	
N03	Antiepileptics	
N04	Anti-parkinson drugs	
N05	Psycholeptics	**A** antipsychotics **B** anxiolytics **C** hypnotics and sedatives
N06	Psychoanaleptics	**A** antidepressants **B** psychostimulants, agents used for adhd and nootropics **C** psycholeptics and psychoanaleptics in combination **D** anti-dementia drugs
N07	Other nervous system drugs	

3. **Active principles**: all the drugs involved in the analysis were named according to the International Nonproprietary Names (INN);[46]

4. **Causality**: the causality assessment is the method by which the extent of relationship between a drug and a suspected reaction is established. It was adopted to exclude from the analysis the doubtful reports of antipsychotics, hypnotics, anxiolytics, antidepressants and stimulants. Currently wide variety of causality assessment scales exist for assessing a possible causal link between a drug treatment and an adverse event in individual patient, each with their own advantages and limitations. In this analysis the reports from Italian and Spain databases have been assessed on the basis of Naranjo score algorithm, while the French reports on the basis of French algorithm. [47,48]

5. **Seriousness**: all serious ADRs were classified according to the WHO definition,[49] as results in:
    - death,
    - life threatening,
    - persistent and severe invalidity,
    - invalidity,
    - congenital anomaly or congenital defect,
    - requires inpatient,
    - hospitalisation and prolongs existing hospitalization.

6. **Age**: the age was subdivided in four classes: ≤ 18 years, 19-59 years, 60-79 years and ≥ 80 years. The reports were excluded if the age was not reported or if the age was under 1 year (in uterus exposure during pregnancy was not considered).

7. **Type of ADRs**: the ADRs were classified by System Organ Class (SOC) and Preferred Terms (PTs) according to WHO-ART hierarchy (World Health Organization Adverse Reaction Terms).[50] As the French ADRs were coded according to the MedDRA (Medical Dictionary for Regulatory Activities) classifications. So, to have a unique coding system, the MedDRA terms were translated into WHO-ART language.[51]

8. **Potentially interacting drugs**. The potential drug-drug interactions (DDIs) were estimated using the Internet version of the DRUGDEX® system for the assessment and classification of drug interactions.[52]

2. Study design: case – non case analysis

The case-non case method, described by van Puijenbroek et al.[51], was applied to investigate if men and women were equally represented in ADR related to psychotropic drug ATC classes of interest (i.e. N05A - antipsychotics, N05B - hypnotics, N05C - anxiolytics, N06A - antidepressants and N06B - stimulants) in comparison with all other drugs.

The “cases” were the spontaneous reports corresponding to the ADRs related at least to one type of ATC classes of psychotropic drugs of interest, reported between 1 January 2007 and 31 December 2009. The non-cases are all reports of ADRs other than that being studied, reported between 1 January 2007 and 31 December 2009.

The association was estimated by calculating a reporting odds ratio (ROR) with its 95% confidence interval (CI).[52]

3. Statistical Analysis

Descriptive statistics for all variables were performed with Microsoft Excel 2007. The reporting odds ratio estimated the strength of the association between the report of ADRs related to psychotropic drugs and sex, the null hypothesis being that men and women were equally distributed whatever the type of drugs involved in the ADRs. The RORs were calculated with their 95% confidence interval (95% CI) as crude reporting odds ratio and reporting odds ratios stratified on classes of age and seriousness, by the Mantel- Haenzel’s method.

Fisher's exact test was used in the analysis of contingency tables whenever the sample size was very small. The level of statistical significance was p-values of <0.05. All the statistical analyses were performed with Epi-Info software (3.5.1 version).

Results

1. Patient characteristics

Altogether, a total of 967 patients were included in the study, after excluding reports where age and/or sex were not available (as well as report concerning patients under 1 year). Of these, 592 (61%) were female while 375 (39%) were male (p< 0,001). The 74% (n = 719) of them were from the Midi-Pyrénées region, while the 13% (n = 130) and the 12% (n = 118) from Veneto and Castilla y León regions, respectively (Table 1).

	Women		Men		Total	
Country	**n°**	**%**	**n°**	**%**	**n°**	**%**
Francia (Midi-Pyrénées)	440	74%	279	74%	719	74%
Italia (Veneto)	73	12%	57	15%	130	13%
Spagna (Castilla y León)	79	13%	39	10%	118	12%
Total	**592**	**100%**	**375**	**100%**	**967**	**100%**

Table 1. Patients distribution by country and by sex.

These 3 regions had an estimated population (Table 2) of approximately 10227170 inhabitants in January 2008 (about 50% of women and 50% of men), and are the main contributors to the French, Italian and Spain spontaneous surveillance system.

	Midi-Pyrénées (Francia)		Veneto (Italia)		Castilla y Leòn (Spagna)	
Sex	**n°**	**%**	**n°**	**%**	**n°**	**%**
Women	1457696	51%	2367445	49%	1287992	50%
Men	1379804	49%	2464895	51%	1269338	50%
Total	**2837500**	**100%**	**4832340**	**100%**	**2557330**	**100%**

Table 2. Distribution of inhabitants in Midi-Pyrénées (France), Veneto (Italy) and Castilla-Leon (Spain) regions (source French census - http://www.insee.fr-; Italian census- http://demo.istat.it/- Spanish census - http://www.ine.es/).

Mean age of the study population was 51 years (range 08-97 years). Men were younger than women with a mean age of 48 ± 12 years (range 09-91 years) and 55 ± 11 years (range 08-97 years), respectively. The difference between them was not statistically significant.

The Table 3 shows the class of age distribution within women and men in all spontaneous reports. There was a significant difference between women and men in all classes except for the 60 - 79 class.

	Women		**Men**		
Age (years)	**n°**	**%**	**n°**	**%**	**p-Value***
≤ 18	12	2%	15	4%	<0,05
19-59	285	48%	210	56%	<0,05
60-79	168	28%	102	27%	NS
≥ 80	127	21%	48	13%	<0,001
Total	**592**	**100%**	**375**	**100%**	

Table 3. Class of age distribution by sex (*χ^2 test: NS = not significant).

Taking into account the seriousness, 47% (n = 452) of patients reported a serious ADR while 53% (n = 515) a not serious ADR (p<0,001). The Table 4 shows the seriousness distribution within women and men in all spontaneous reports. Significantly difference was observed in serious and not serious ADRs between women and men.

	Women		**Men**		**p-Value***
Seriousness	**n°**	**%**	**n°**	**%**	
Serious ADRs	275	46%	177	47%	<0,001
Non serious ADRs	317	54%	198	53%	<0,001
Total	**592**	**100%**	**375**	**100%**	

Table 4. Seriousness distribution by sex (*χ^2 test).

2.“Case/non case” comparison

Table 5 shows the main characteristics of patients included in the study and all other patients (non-cases).

Percentage of women and patients age with 19-59 years and over 80 years were significantly higher in patients with the selected psychotropic drugs ADRs in comparison with other drugs ADRs (non-cases). The same was observed for the serious ADRs, which appeared more frequent in patients who reported spontaneous ADRs after the use of antipsychotics, hypnotics, anxiolytics, antidepressants and stimulants.

This could be explained by the higher consumption of psychotropic drugs in women, because the pattern of use of drugs is influenced by age (eg. vaccine and children) or simply by the different pharmacodynamics and pharmacokinetics of the drugs.

	Patients with psychotropic drug ADRs (N = 967)		**Patients with other drug ADRs (N=9228)**		
	n°	**% (95% CI)**	**n°**	**% (95% CI)**	**p –Value**
Sex					
Women	592	61,2% (58,1-64,3)	5193	56,3% (55,3-57,3)	<0,05
Age (years)					
≤ 18	27	2,9% (1,8-4,0)	1445	15,7% (14,9-16,4)	<0.001
19-59	495	53,4% (50,2-56,6)	3643	39,5% (38,5-40,5)	<0.001
60-79	270	29,1% (26,2-32,1)	2833	30,7% (29,8-31,6)	NS
≥ 80	175	18,9% (16,4-21,4)	1307	14,2% (13,5-14,9)	<0.001
Seriosness					
Serious	452	48,8% (45,5-52,0)	3584	38,8% (37,8-39,8)	<0.001

Table 5. Distribution by sex, age and seriousness ADRs in patients with psychotropic drug ADRs of interest (reports of N05A/ N05B/ N05C/ N06A/ N06B) and in patients with other drug ADRs (all reports excluded N05A, N05B, N05C, N06A, N06B) (*χ^2 test: NS = not significant).

Because some patients took one or more class of medications (antipsychotics, hypnotics, antidepressants and stimulants) simultaneously, the total number of cases were greater than the total number of patients having a reaction.

Table 6a shows the sex distribution of cases within each ATC class. The difference between women and men was significantly more associated with

antipsychotics (p<0,001), anxiolytics (p<0,001), hypnotics (p<0,001) and antidepressants (p<0,001). The Table 6b illustrates the ROR crude and stratified calculated in order to investigate if men and women were equally represented in reports of ADRs related to a single ATC class of psychotropic drugs (cases) in comparison with all reports of ADR related to other drugs (non-cases).
The crude and stratified ROR were significantly (p< 0,001) associated with female sex in only the N06A drug class (antidepressants) (ROR crude =1,67; 95% CI 1,35-2,06; ROR stratified for seriousness =1,71; 95% CI 1,39-2,11; ROR stratified for age = 1,53; 95% CI 1,24-1,90; ROR stratified for age and seriousness =1,54; 95% CI 1,25-1,90).

		Women		Men		
	n°total reports	**n°**	**%***	**n°**	**%***	**p-Value****
N05A	405	229	57%	176	43%	p<0,001
N05B	225	132	59%	93	41%	p<0,001
N05C	148	89	60%	59	40%	p<0,001
N06A	444	303	68%	141	32%	p<0,001
N06B	21	13	62%	8	38%	NS
Total	**1243**	**766**		**477**		

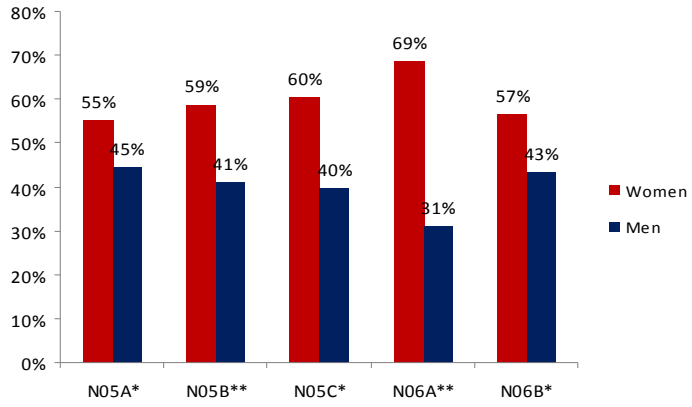
Table 6a. Sex distribution of cases within each ATC class (* the percentage was calculated within each single ATC class;**χ2 test: NS = not significant).

ATC	Crude ROR (95% IC)	p -Value	ROR (95% IC)$^{\alpha}$	p - Value$^{\alpha}$	ROR (95% IC)$^{\beta}$	p - Value$^{\beta}$	ROR (95% IC)$^{\gamma}$	p - Value $^{\gamma}$
N05A	1,01	NS	1,04	NS	0,93	NS	0,94	NS
	(0,82-1,24)		(0,84-1,27)		(0,76-1,15)		(0,76-1,16)	
N05B	1,10	NS	1,14	NS	1,02	NS	1,04	NS
	(0,84-1,46)		(0,86-1,50)		(0,77-1,35)		(0,79-1,38)	
N05C	1,17	NS	1,21	NS	1,08	NS	0,74	NS
	(0,83-1,65)		(0,86-1,71)		(0,77-1,53)		(0,53-1,04)	
N06A	**1,67**	**<0,001**	**1,71**	**<0,001**	**1,53**	**<0,001**	**1,54**	**<0,001**
	(1,35-2,06)		**(1,39-2,11)**		**(1,24-1,90)**		**(1,25-1,90)**	
N06B	1,26	NS	1,31	NS	1,47	NS	1,57	NS
	(0,49-3,33)		(0,51-3,44)		(0,56-3,85)		(0,58-4,12)	

Table 6b. Crude and stratified ROR calculated according to case non-case method. ($^{\alpha}$ stratified for seriousness; $^{\beta}$ stratified for class of age; $^{\gamma}$ stratified for class of age and seriousness; ROR = reporting odds ratio).

3. Type of drugs distribution

Because some patients taken simultaneously one or more drugs belonging to the same ATC class of psychotropic medications, the total number of active principles suspected were greater than the total number of cases. This explains the fact that 1344 active principles were detected, 61% (n = 821) taken by women and 39% (n = 523) by men (p< 0,001). Of the total number of drugs the most involved were belonged to N05A class (antipsychotics) (n = 487; 36%) and antidepressants (N06A) (n = 460; 34%). Anxiolytics (N05B), hypnotics (N05C) and stimulants (N06B) represented the 17% (n = 223), the 11% (n = 151) and the 2% (n = 23) of the 1344 drugs, respectively. Graphic 1 shows the sex distribution of the different class of suspected drugs according the ATC code. The difference between women and men was significantly more associated with antipsychotics (p<0,05), anxiolytics (p<0,001), hypnotics (p<0,05), antidepressants (p<0,001) and stimulants (p<0,05).



Graphic 1. Sex distribution of drugs according to ATC code. The percentage was calculated within each single ATC class (* = p<0,05; ** = p<0,001; χ2 test)

The most involved active principles were risperidone (14 % of the total N05A drugs), alprazolam (14 % of the total N05B drugs), zolpidem (32% of the total N05C drugs), paroxetine (16 % of the total N06A drugs) and methylphenidate (39% of the total N06B drugs), while the most associated with female sex, were lithium carbonate (p<0,05) and prazepam (p<0,05), and with male sex were clozapine (p<0,05) and sertraline (p<0,05). The distribution of the active principles belonging to their ATC class are reported in the Tables 7,8,9,10 and 11.

	Women		Men		
Active principles	**n°**	**%**	**n°**	**%**	**p-Value****
risperidone	40	15%	26	12%	NS
olanzapine	34	13%	25	11%	NS
cyamemazine*	27	10%	29	13%	NS
loxapine*	26	10%	18	8%	NS
aripiprazole	22	8%	16	7%	NS
lithium carbonate	**21**	**8%**	**6**	**3%**	**<0,05**
haloperidol	19	7%	17	8%	NS
clozapine	**11**	**4%**	**21**	**10%**	**<0,05**
amisulpride	10	4%	4	2%	NS
veralipride	8	3%	0	0%	NS
quetiapine	7	3%	6	3%	NS
levomepromazine	6	2%	11	5%	NS
sulpiride	5	2%	1	0%	NS
fluphenazine	4	1%	3	1%	NS
tiapride	4	1%	10	5%	NS
zuclopenthixol	4	1%	4	2%	NS
paliperidone	3	1%	3	1%	NS
periciazine	3	1%	3	1%	NS
pipotiazine	3	1%	1	0%	NS
ziprasidone	3	1%	0	0%	NS
chlorpromazine	2	1%	4	2%	NS
levosulpiride	2	1%	1	0%	NS
pimozide	2	1%	1	0%	NS
droperidol	1	0%	0	0%	NS
pipamperone	1	0%	2	1%	NS
tetrabenazine	1	0%	1	0%	NS
clotiapine	0	0%	2	1%	NS
flupentixol	0	0%	3	1%	NS
Total	**269**	**100%**	**218**	**100%**	

Table 7. Antipsychotics active principles distribution by sex (*Cyamemazine and loxapine are available only in the French market; ** = χ^2 test: NS = not significant).

	Women		Men		
Active principles	**n°**	**%**	**n°**	**%**	**p-Value***
alprazolam	20	15%	11	12%	NS
bromazepam	18	14%	11	12%	NS
oxazepam	18	14%	13	14%	NS
hydroxyzine	15	11%	11	12%	NS
meprobamate	14	11%	13	14%	NS
prazepam	**15**	**11%**	**1**	**1%**	**<0,05**
clorazepate potassique	8	6%	12	13%	NS
lorazepam	8	6%	8	9%	NS
diazepam	5	4%	9	10%	NS
clobazam	3	2%	2	2%	NS
clotiazepam	3	2%	0	0%	NS
etifoxine	3	2%	0	0%	NS
halazepam	1	1%	1	1%	NS
Total	**131**	**100%**	**92**	**100%**	

Table 8. Anxiolytics active principles distribution by sex (* χ^2 test: NS = not significant).

	Women		Men		
Active principles	**n°**	**%**	**n°**	**%**	**p-Value****
zolpidem	29	32%	20	33%	NS
zopiclone	26	29%	13	22%	NS
Meprobamate + acepromethazine*	24	26%	11	18%	NS
midazolam	6	7%	8	13%	NS
lormetazepam	5	5%	3	5%	NS
temazepam	1	1%	0	0%	NS
flunitrazepam	0	0%	1	2%	NS
lorazepam	0	0%	1	2%	NS
triazolam	0	0%	1	2%	NS
valeriane	0	0%	2	3%	NS
total	**91**	**100%**	**60**	**100%**	

Table 9. Hypnotics active principles distribution by sex (* = The association between meprobamate + acepromethazine is available only in France; ** χ^2 test: NS = not significant).

	Women		Men		
Active principles	**n°**	**%**	**n°**	**%**	**p-Value***
paroxetine	46	15%	28	20%	NS
duloxetine	45	14%	19	13%	NS
escitalopram	40	13%	18	13%	NS
venlafaxine	37	12%	17	12%	NS
citalopram	28	9%	11	8%	NS
amitriptyline	23	7%	9	6%	NS
fluoxetine	19	6%	7	5%	NS
mirtazapine	20	6%	10	7%	NS
clomipramine	12	4%	4	3%	NS
bupropion	11	3%	2	1%	NS
mianserine	8	3%	0	0%	NS
sertraline	11	3%	12	8%	**<0,05**
tianeptine	6	2%	1	1%	NS
dosulepine	2	1%	0	0%	NS
milnacipran	2	1%	4	3%	NS
trazodone	3	1%	0	0%	NS
fluvoxamine	1	0%	1	1%	NS
imipramine	1	0%	0	0%	NS
moclobemide	1	0%	0	0%	NS
rivastigmine	1	0%	0	0%	NS
Total	**317**	**100%**	**143**	**100%**	

Table 10. Antidepressants active principles distribution by sex (* χ^2 test: NS = not significant).

	Women		Men		
Active principles	**n°**	**%**	**n°**	**%**	**p-Value***
methylphenidate	4	31%	5	50%	NS
levocarnitine acetyl	2	15%	0	0%	NS
modafinil	2	15%	1	10%	NS
atomoxetina	1	8%	3	30%	NS
cytidine + uridine	1	8%	0	0%	NS
deanol pidolate	1	8%	0	0%	NS
heptaminol	1	8%	0	0%	NS
piracetam	1	8%	1	10%	NS
Total	**13**	**100%**	**10**	**100%**	

Table 11. Stimulants active principles distribution by sex (* χ^2 test: NS = not significant).

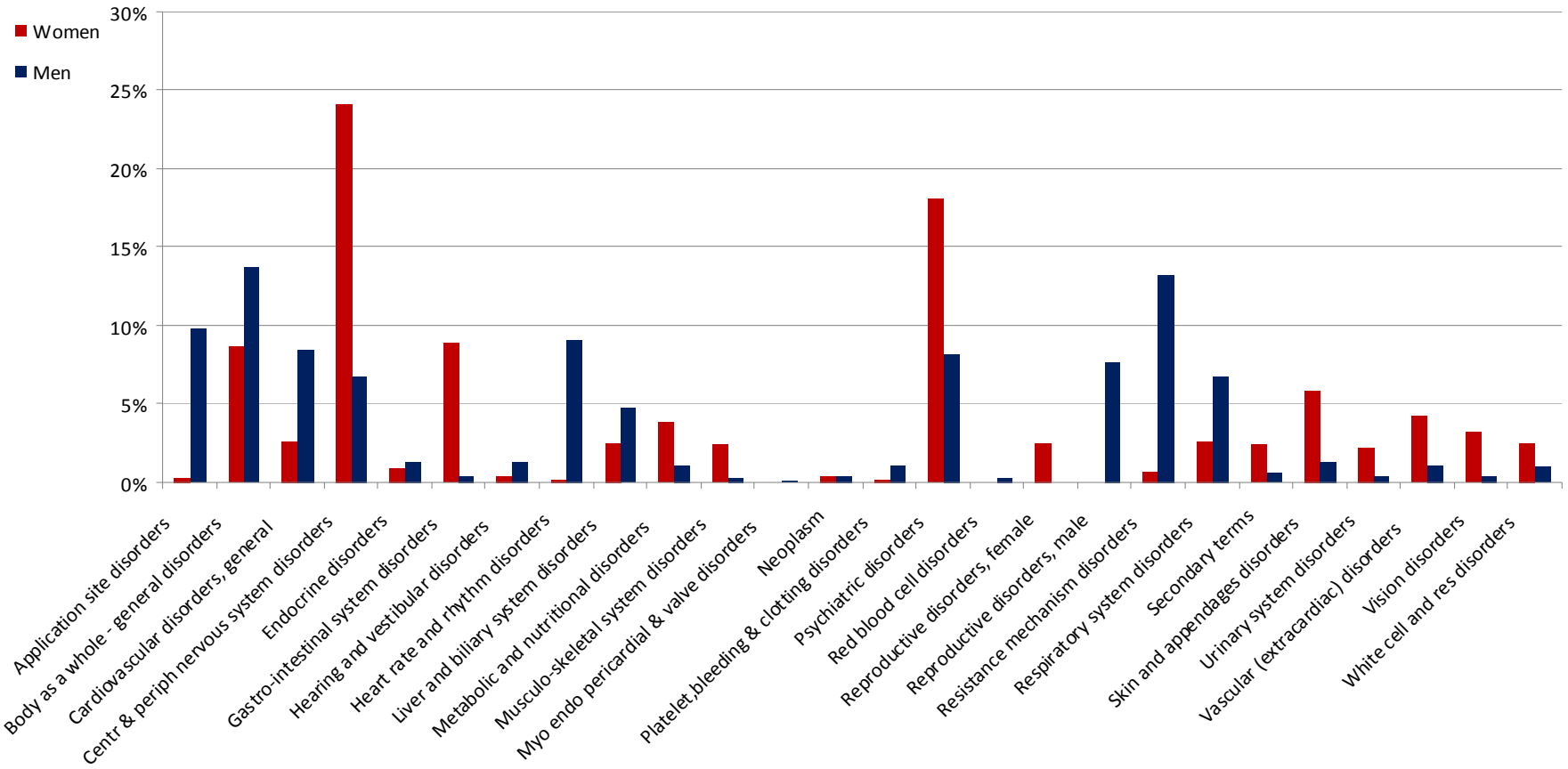
4. Type of ADRs distribution

Because of some patients had several ADRs simultaneously or successively, the total number of reactions were greater than the total number of patients having a reaction. This explains the fact that among the 967 spontaneous reports selected from the databases 1835 ADRs were detected, 60% in women and 40% in men (p< 0,001).

Graphic 2 shows the System Organ Class (SOC) classified according to the WHO-ART (World Health Organization Adverse Reaction Terms)[49] hierarchy distribution of all reports of the suspected drugs. The most frequent type of ADRs reported in all women reports were classified as “Central & peripherical nervous system disorders” (24%; n = 268) and “Psychiatric disorders” (18%; n°= 201), while the most frequent type of ADRs reported in all men reports were classified as “Body as a whole - general disorders” (14%; n°= 95) and “Resistance mechanism disorders” (13%; n°= 92).

Analyzing the distribution of all SOC terms, irrespective of the type of psychotropic drugs, the difference between women and men was significantly more associated with women for all the SOC except for “Endocrine disorders, Hearing and vestibular disorders, Myo -endo pericardial & valve disorders, neoplasm, platelet, bleeding & clotting disorders, Red blood cell disorders”.

This trend changed if the comparison was made between women and men within each ATC class. The terms more associated with sex, in particular with women, were: “Poison specific terms” (p<0.001) and “Cardiovascular disorders, general” (p<0.001) in N05A (antipsychotics); “Central & peripherical nervous system disorders” (p<0.05) in N05C ATC (hypnotics); “Psychiatric disorders” (p<0.001) in N06A (antidepressants). No SOC terms belonging to N05B (anxiolytics) and N06B (stimulants) were significantly associated with women.



Graphic 2. Sex distribution of spontaneous reports according to the SOC (WHO-ART hierarchy).[49]

5. Focus on drugs

Analyzing the distribution of active principles within each class of psychotropic medications, as was previously described, risperidone, alprazolam, zolpidem and paroxetine are the most involved drugs both in women and in men. The reflection upon these active principles should necessarily link up with the population consumption. At the time of data analysis not all these data were available, so we postpone this investigation to a subsequent work.

Nevertheless, to understand the potentiality of the data detected from the spontaneous reporting system, we performed a “focus” analysis on risperidone, alprazolam and paroxetine.

Risperidone (antipsychotics - N05A)

Among the 967 patients selected in this study 66 took risperidone, of these the 61% (n =40) were women and the 39% (n°= 26) men ($p < 0.05$). The 85% (n°=56) of all risperidone ADRs derived from the French spontaneous database, the 9% (n=6) from the Spanish and the 6% (n = 4) from the Italian databases.

Women were younger than men with a mean age of 69 years (range 38-96 years) and 78 years (range 72-88 years), respectively (difference no statistically significant).

Taking into account the seriousness, 53% (n°= 35) of ADRs were serious and 47% (n°= 31) non serious (difference non statistic ally significant) (Table 12).

	Women		**Men**		**p-Value***
Seriousness	**n°**	**%**	**n°**	**%**	
Serious	21	53%	14	54%	NS
Non serious	19	48%	12	46%	NS
Total	**40**	**100%**	**26**	**100%**	

Table 12. Seriousness distribution by sex (*$\chi 2$ test: NS = non significant).

The severe ADRs more often result, both in women and in men, in the hospitalization (or increase in the duration of the hospitalization). Two deaths were reported: a 85 years old woman with a “circulatory failure” adverse reaction and a 55 years old woman with a “dysphagia” adverse reaction.

Analyzing the distribution of the type of SOC terms, “Central & peripherical nervous system disorders” and “Psychiatric disorders” were the most reported, respectively of the 27% and 14% (Table 13). No SOC terms belonging to risperidone ADRs were significantly associated with women.

	Total		Women		Men	
System Organ Class (SOC) terms	**n°**	**%**	**n°**	**%**	**n°**	**%**
Application site disorders	2	3%	0	0%	2	7%
Body as a whole - general disorders	7	9%	3	6%	4	14%
Cardiovascular disorders, general	3	4%	2	4%	1	4%
CNS & peripherical nervous system disorders	**21**	**27%**	**14**	**28%**	**7**	**25%**
Endocrine disorders	2	3%	0	0%	2	7%
Gastro-intestinal system disorders	7	9%	6	12%	1	4%
Heart rate and rhythm disorders	2	3%	1	2%	1	4%
Liver and biliary system disorders	2	3%	0	0%	2	7%
Metabolic and nutritional disorders	5	6%	4	8%	1	4%
Musculo-skeletal system disorders	2	3%	0	0%	2	7%
Neoplasm	1	1%	1	2%	0	0%
Platelet,bleeding & clotting disorders	1	1%	1	2%	0	0%
Psychiatric disorders	**11**	**14%**	**10**	**20%**	**1**	**4%**
Red blood cell disorders	2	3%	0	0%	2	7%
Secondary terms	4	5%	3	6%	1	4%
Skin and appendages disorders	2	3%	2	4%	0	0%
Urinary system disorders	1	1%	1	2%	0	0%
Vascular (extracardiac) disorders	1	1%	1	2%	0	0%
Vision disorders	2	3%	1	2%	1	4%
Total	**78**	**100%**	**50**	**100%**	**28**	**100%**

Table 13. Distribution of SOC terms by sex (World Health Organization Adverse Reaction Terms).[50]

Within the “Central & peripherical nervous system disorders” and “Psychiatric disorders”, the most reported preferred terms were “Extrapyramidal disorder” (33%, n =7) and “Confusion” (45%, n =5) (Tables 14a, 14b). All these two type of reactions were reported in the literature (source DRUGDEX), [51] but only extrapyramidal were reported in adult patients receiving risperidone therapy with an incidence of 7% to 31%.

Tacking into account the ADRs most associated with female sex, two cases of hyponatraemia, one of CPK-increased and one of polydipsia were found in the "Metabolic and nutritional disorders" SOC class. One case of circulatory failure (the death previously described),one case of hypotension and one case of QT prolonged were carried out from the female "Cardiovascular disorders" and "Heart rate and rhythm disorders" ADRs reported in the reports.

CNS & peripherical nervous system disorders	**Women**		**Men**	
Preferred Term	**n°**	**%**	**n°**	**%**
Aphasia	1	7%	0	0%
Convulsions	1	7%	1	14%
Dyskinesia	2	14%	1	14%
Encephalopathy	1	7%	0	0%
Extrapyramidal disorder	**6**	**43%**	**1**	**14%**
Hyperkinesia	0	0%	1	14%
Muscle rigidity	1	7%	0	0%
Neuroleptic malignant syndrome	2	14%	3	43%
Total	**14**	**100%**	**7**	**100%**

Table 14 a. "CNS & peripherical nervous system disorders" distribution by sex (World Health Organization Adverse Reaction Terms).[49]

Psychiatric disorders	**Women**		**Men**	
Preferred Term	**n°**	**%**	**n°**	**%**
Agitation	1	10%	0	0%
Catatonic reaction	2	20%	0	0%
Confusion	**4**	**40%**	1	100%
Paranoid delusions	1	10%	0	0%
Somnolence	2	20%	0	0%
Total	10	100%	1	100%

Table 14 b. "Psychiatric disorders" distribution by sex (World Health Organization Adverse Reaction Terms).[49]

The distribution of the drugs took simultaneously with risperidone is shown in the Tables 15 a/b. Except for haloperidol, all the concomitant drugs have caused serious adverse reactions. More than one concomitant medication was taken in two women (i.e. biperiden/ clodronic acid and furosemide/zopiclone/meprobamate) and in one man (i.e. paliperidone/venlafaxine/lorazepam). A potential drug-drug interactions (DDIs) was estimated for the combination of risperidone + haloperidol and risperidone + quetiapine.

	Women		Men		
Concomitant drugs	**n°**	**%**	**n°**	**%**	**p-Value***
Yes	4	10%	3	12%	NS
No	36	90%	23	88%	<0,05
Total	**40**	**100%**	**26**	**100%**	

Table 15 a. Concomitant distribution by sex (*χ^2 test: NS = non significant).

Sex	Type of concomitant drugs	Severe ADRs	DDIs*	PTs**	Interaction Effect reported*
Women	**biperiden**	Yes	No		
	clodronic acid	Yes	No		
	furosemide	Yes	No		
	haloperidol	No	Yes	Hypotension	Cardiotoxicity
	meprobamate	Yes	No		
	zopiclone	Yes	No		
	quetiapine	Yes	Yes	Haematuria	Cardiotoxicity
Men	**delorazepam**	Yes	No		
	lorazepam	Yes	No		
	metilfenidate	Yes	No		
	paliperidone	Yes	No		
	venlafaxine	Yes	No		

Table 15 b. Concomitant drugs description (*Potential drug-drug interactions (DDIs) estimated in DRUGDEX;[42] ** Preferred Terms (PTs) according to WHO-ART hierarchy [50]).

Alprazolam (anxiolytics - N05B)

Among the 967 patients selected in this study, 31 took alprazolam, of these the 65% (n°=20) were women and the 35% (n°= 11) were men (p<0,05). Of these drugs 77% (n°=24) derived from the French spontaneo us database, 13% (n°=4) from the Spanish database and the 10% (n°= 3) from the Italian database. Women were older than men with respectively a mean age of 59 years (range 13-88 years) and 49 years (range 23-86 years) (difference no statistically significant). Taking into account the seriousness, 53% (n°= 35) of ADRs were serious and 47% (n°= 31) non serious (difference non statistic ally significant) (Table 16).

	Women		Men		p-Value*
Seriousness	**n°**	**%**	**n°**	**%**	
Serious	10	50%	7	64%	NS
Non serious	10	50%	4	36%	<0,05
Total	**20**	**100%**	**11**	**100%**	

Table 16. Seriousness distribution by sex (*χ^2 test: NS = non significant).

The severe ADRs more often result, both in women and in men, in the hospitalization (or increase in the duration of the hospitalization). One death was reported: a 46 years old woman who went into a “coma” (this woman took both paroxetine and alprazolam).

Analyzing the distribution of the SOC terms, “Central & peripherical nervous system disorders” and “Body as a whole - general disorders” were the most reported (Table 17). No SOC terms belonging alprazolam ADRs were significantly associated with women.

	Total		Women		Men	
System Organ Class (SOC) terms	**n°**	**%**	**n°**	**%**	**n°**	**%**
Body as a whole - general disorders	**9**	**20%**	**6**	**19%**	**3**	**21%**
Cardiovascular disorders, general	3	7%	1	3%	2	14%
CNS & peripherical nervous system disorders	**9**	**20%**	**9**	**28%**	**0**	**0%**
Gastro-intestinal system disorders	3	7%	3	9%	0	0%
Liver and biliary system disorders	1	2%	0	0%	1	7%
Metabolic and nutritional disorders	1	2%	0	0%	1	7%
Musculo-skeletal system disorders	1	2%	1	3%	0	0%
Null	2	4%	1	3%	1	7%
Psychiatric disorders	8	17%	6	19%	2	14%
Secondary terms	3	7%	1	3%	2	14%
Skin and appendages disorders	5	11%	3	9%	2	14%
Vision disorders	1	2%	1	3%	0	0%
Total	**46**	**100%**	**32**	**100%**	**14**	**100%**

Table 17. Distribution of SOC terms by sex (World Health Organization Adverse Reaction Terms).[50]

Most of the reactions reported in the Tables 18 a/b have been reported in the literature as neurological effects (source DRUGDEX).[51]

CNS & peripherical nervous system disorders	**Women**		**Men**	
Preferred Term	**n°**	**%**	**n°**	**%**
Balance difficulty	1	11%	1	17%
Coma	2	22%	1	17%
Convulsions	0	0%	1	17%
Extrapyramidal disorder	1	11%	1	17%
Headache	1	11%	0	0%
Paraesthesia	1	11%	1	17%
Tremor	1	11%	1	17%
Vertigo	2	22%	0	0%
Total	**9**	**100%**	**6**	**100%**

Table 18 a. "CNS & peripherical nervous system disorders" distribution by sex (World Health Organization Adverse Reaction Terms).[50]

Body as a whole - general disorders	**Women**		**Men**	
Preferred Term	**n°**	**%**	**n°**	**%**
Death	1	17%	0	0%
Drug level decreased	0	0%	1	33%
Fatigue	1	17%	0	0%
Hypersensitivity	1	17%	0	0%
Malaise	2	33%	2	67%
Pallor	1	17%	0	0%
Total	**6**	**100%**	**3**	**100%**

Table 18 b "Body as a whole - general disorders" distribution by sex (World Health Organization Adverse Reaction Terms).[50]

The distribution of the concomitant drugs is shown in the Tables 19 a/b. More than one concomitant medication was taken in two women: one reported 2 concomitant drugs which were composed respectively by two type of molecules (i.e. ketorolac+omeprazole/amiloride + hidroclorotiazide) and the other reported 3 concomitants drugs (i.e. duloxetine /betahistine /omeprazole). As can be seen, all these drugs except for duloxetine, escitalopram, lercanidipine have caused serious adverse reactions.

	Women		**Men**		
Concomitant drugs	**n°**	**%**	**n°**	**%**	**p-Value***
Yes	5	25%	1	9%	NS
No	15	75%	10	91%	NS
Total	**20**	**100%**	**11**	**100%**	

Table 19 a. Concomitant distribution by sex (*χ^2 test: NS = non significant).

A potential drug-drug interactions (DDIs) was estimated for the combination of alprazolam + omeprazole and alprazolam + magnesium pidolate.

Sex	**Type of concomitant drugs**	**Severe ADRs**	**DDIs***	**PTs****	**Interaction Effect reported***
Women	duloxetine	No	No		
	duloxetine	Yes	No		
	betahistine	Yes	No		
	omeprazole	Yes	Yes	Malaise	Benzodiazepine toxicity (CNS depression, ataxia, lethargy)
	ketorolac+omeprazole	Yes	No		
	lercanidipine	No	No		
	magnesium pidolate	Yes	No	Haematuria	Cardiotoxicity
	amiloride+ hidroclorotiazide	Yes	No		
Men	escitalopram	No	No		

Table 19 b. Concomitant drugs description (*Potential drug-drug interactions (DDIs) estimated in DRUGDEX;[42] ** Preferred Terms (PTs) according to WHO-ART hierarchy[50]).

Paroxetine (antidepressants - N06A)

Among the 967 patients selected in this study, 74 took paroxetine, of these the 62% (n°=46) were women and the 38% (n°= 28) were men (p<0,001). The 89% (n°=66) of all ADRs derived from the French spontaneous database, the 8% (n°=6) from the Spanish and the 3% (n°= 2) from the Italian database. Mean age was similar in women and in men, respectively of 60 years (range 15-96 years) and 57 years (range 22-88 years) (difference no statistically significant).

Taking into account the seriousness, 45% (n°= 33) of ADRs were serious and 55% (n°= 41) non serious (difference non statistically significant) (Table 20).

	Women		Men		p-Value*
Seriousness	**n°**	**%**	**n°**	**%**	
Serious	20	43%	13	46%	NS
Non serious	26	57%	15	54%	<0,05
Total	**46**	**100%**	**28**	**100%**	

Table 20. Seriousness distribution by sex (*χ2 test: NS = non significant).

The severe ADRs more often result, both in women and in men, in the hospitalization (or increase in the duration of the hospitalization). Two deaths were reported: a 46 years old woman who went into a “coma” (this woman took both paroxetine and alprazolam) and a 76 years old woman with a general “hemorrhage” adverse reaction.

Analyzing the distribution of SOC terms, “Central & peripherical nervous system disorders” and “Psychiatric disorders” were the most reported SOC class, respectively of the 15% and 16% (Table 21). No SOC terms were significantly associated with women.

	Total		Women		Men	
System Organ Class (SOC) terms	**n°**	**%**	**n°**	**%**	**n°**	**%**
Application site disorders	1	1%	1	2%	0	0%
Body as a whole - general disorders	10	12%	8	14%	2	7%
Cardiovascular disorders, general	1	1%	1	2%	0	0%
CNS & peripherical nervous system disorders	**13**	**15%**	**10**	**18%**	**3**	**10%**
Endocrine disorders	3	3%	2	4%	1	3%
Gastro-intestinal system disorders	8	9%	5	9%	3	10%
Heart rate and rhythm disorders	1	1%	1	2%	0	0%
Liver and biliary system disorders	3	3%	1	2%	2	7%
Metabolic and nutritional disorders	9	10%	7	12%	2	7%
Null	1	1%	0	0%	1	3%
Platelet,bleeding & clotting disorders	9	10%	5	9%	4	14%
Psychiatric disorders	**14**	**16%**	**8**	**14%**	**6**	**21%**
Red blood cell disorders	1	1%	0	0%	1	3%
Reproductive disorders, female	3	3%	3	5%	0	0%
Respiratory system disorders	1	1%	0	0%	1	3%
Secondary terms	4	5%	3	5%	1	3%
Skin and appendages disorders	2	2%	1	2%	1	3%
Urinary system disorders	1	1%	1	2%	0	0%
Vision disorders	1	1%	0	0%	1	3%
Total	**86**	**100%**	**57**	**100%**	**29**	**100%**

Table 21. Paroxetine type of ADRs distribution by sex (World Health Organization Adverse Reaction Terms).[50]

Most of the ADRs classified as “Central & peripherical nervous system disorders” and “Psychiatric disorders” (Tables 22 a/b) were reported in the literature (source DRUGDEX)[51] (confusion –incidence 1% -dizziness - incidence: 6% to 14%; extrapyramidal sign – incidence >10%; headache - incidence 17% to 27%; insomnia - incidence > 24%; somnolence – incidence > 24%; tremor -incidence: 4% to 11%; anxiety -incidence: > 5%).

	Women		Men	
Preferred Term	**n°**	**%**	**n°**	**%**
Coma	1	8%	0	0%
Dizziness	1	8%	0	0%
Dyskinesia	2	17%	0	0%
Extrapyramidal disorder	1	8%	0	0%
Headache	1	8%	0	0%
Neuroleptic malignant syndrome	1	8%	0	0%
Tremor	1	8%	0	0%
Vertigo	**4**	**33%**	**1**	**8%**
Total	**12**	**100%**	**1**	**100%**

Table 22 a. "CNS & peripherical nervous system disorders" distribution by sex(World Health Organization Adverse Reaction Terms).[50]

Vertigo and somnolence were the most reported preferred terms of the "Central & peripherical nervous system disorders" and "Psychiatric disorders" SOC classes.

	Women		Men	
Preferred Term	**n°**	**%**	**n°**	**%**
Anxiety	0	25%	2	33%
Confusion	1	25%	2	33%
Drug dependence	1	0%	0	0%
Insomnia	0	13%	1	17%
Personality disorder	1	0%	0	0%
Somnolence	**5**	**0%**	**1**	**17%**
Total	**8**	**100%**	**6**	**100%**

Table 22 b. "Psychiatric disorders" distribution by sex (World Health Organization Adverse Reaction Terms).[50]

The distribution of the concomitant drugs is shown in the Tables 23 a/b. The combinations of paroxetine and bromazepam, cyanemazine, digoxin, lansoprazole, nitroglycerin and serenoa repens have caused serious adverse reactions. More than one concomitant medication was taken in three women (i.e. risperidone/lorazepam/maprotiline/lamotrigine; and nitroglycerin/digoxin/cyamemazine; and fluvastatin/acetylsalicylic acid) and in two men (i.e. simvastatin/aceclofenac; and lansoprazole/serenoa repens/lamotrigine; and bromazepam, cyamemazine). A potential drug-drug interactions (DDIs) was estimated for the association between paroxetine + risperidone.

	Women		Men		
Concomitant drugs	**n°**	**%**	**n°**	**%**	**p-Value***
Yes	8	17%	8	29%	NS
No	38	83%	20	71%	<0,001
Total	**46**	**100%**	**28**	**100%**	

Table 23 a. Concomitant distribution by sex (*χ^2 test: NS = non significant).

Sex	**Type of concomitant drugs**	**Severe**	**DDIs***	**PTs****	**Interaction Effect reported***
Women	**aceclofenac**	No			
	alprazolam	No			
	bromazepam	Yes			
	clorazepate potassique	No			
	cyamemazine	Yes			
	digoxin	Yes			
	fluvastatin	No			
	lamotrigine	No			
	lansoprazole	Yes			
	lercanidipine	No			
Men	**acetylsalicylic acid**	No			
	lorazepam	No			
	lormetazepam	No			
	maprotiline	No			
	mirtazapine	No			
	nitroglycerin	Yes			
	prednisone	No			
	rabeprazolo	No			
	risperidone	No	Yes	Haematoma	Increased plasma concentrations of risperidone and an increased risk of risperidone adverse effects such as serotonin syndrome, QT prolongation, and extrapyramidal effects.
	serenoa repens	Yes			
	simvastatin	No			

Table 23 b. Concomitant drugs description (*Potential drug-drug interactions (DDIs) estimated in DRUGDEX;[42] ** Preferred Terms (PTs) according to WHO-ART hierarchy[50]).

Discussion

1. Overall sample of patients

To our knowledge, this is the first multinational prospective study focused on gender differences in spontaneously reported ADRs to pharmacovigilance systems. The opportunity to combine data from 3 different areas in Europe has facilitated the detection of a large number of ADRs related to psychotropic medications (antipsychotics, hypnotics, antidepressants and stimulants) (about one thousand cases on 3 years).

However the most of the spontaneous reports derived from France. Differences observed in the three countries for the number of ADRs and for some drugs could be partly explained by difference in reporting rates, availability of drugs in different countries, prescribing attitudes, reimbursement scheme, or by environmental or genetic factors.[43]

The question as to whether ADR occurrence depends on gender is controversially and ambiguously discussed in the literature. [53-57] Gender-specific differences in drug susceptibility are often assumed, [15,17,19] but the evidence is limited, because to date, sex differences in adverse effects have not been well studied, especially in the spontaneously pharmacovigilance systems.[8]

Our data suggest that women are more prone than men to experiencing of psychotropic drugs-induced adverse effects when they are young, middle-aged or very old. The association between the higher ADR risk in elderly women have also been observed by other investigators. [11,15,19,53- 58] Polipharmacy exposure, age-related changes in pharmacokinetics and pharmacodynamics, higher prevalence of chronic conditions and geriatric syndromes (eg, cognitive impairment, gait instability, benign prostatic hypertrophy), together with the potentially inappropriate prescription, place elders at increased risk of experiencing adverse drug events well as worse outcomes should these events occur.[60,61] This appears more frequent in women than in men, also because women are more prone to use inappropriately the drug therapy.[60]

In the case of young and middle-aged women, the correlation between the occurrence of the adverse reactions and the female sex, might be explained taking into account psychotropic drugs use, female pharmacokinetics and

pharmacodynamics, and all other factors described as “gender” attributes (see the introduction).

In our analysis, antipsychotics, including mood stabilizers, and antidepressants are the most reported medications. After the case/non-case comparison, the association with the use of psychotropic medications of interest and women appears only in antidepressant drugs, irrespective of the seriousness and/or age, with consequent psychiatric effects on women mental health.

Our findings are in line with the published literature, which reveals certain differences in frequency and/or seriousness of adverse effects of antipsychotics and antidepressants.[9]

The health burden of antipsychotic medication is well known, but the disproportionate effect on women as compared with men is underappreciated.[62,63] In general, female patients experience fewer negative symptoms, better social adaptation, a better response to lower doses of antipsychotic medication, fewer inpatient admissions and hospitalizations compared to men.[63]

However, the reasons for this increased risk in female patients are not entirely clear but include “gender” and “sex” related differences in the use of medications.[63]

Adverse drug reactions are important determinants of non-adherence to antidepressant treatment, but their assessment is complicated by overlap with depressive symptoms and lack of reliable self-report measures.[64] It has been previously reported that adverse reactions are more frequently experienced by individuals with more severe depression. [64] In fact, patients with severe depressive symptoms are more likely to experience physical adverse reactions to antidepressants. [64] This may be because of the increased sensitivity and attention to physical discomfort that accompanies depressed mood. [64-67]

In a recent study, Keers R. reported that the suicidal ideation may be dependent with both antidepressant treatment and gender.[68] Gender-specific effects on suicidal ideation, particularly highlighted for nortriptyline, a second-generation tricyclic antidepressant (TCA), may be result of an exacerbation of the irritable symptoms more often observed in men with depression.[68]

The reflection upon the antipsychotics and antidepressants might be deepened considering the fact that during the last 20 years, new-generation of

antidepressant and antipsychotics have undoubtedly increased the therapeutic options available for patients suffering from psychiatric disorders.[32] Their claims of better efficacy/tolerability profile have contributed to a progressive increase in sales and consumption of novel drugs which might be responsible of the increase of adverse reactions. [32]

2. Drugs strongly related to the occurrence of ADRs.

It is well known that lithium carbonate, a cornerstone drug of treatment in bipolar disorders, can cause adverse drug reactions, especially in women.[9] A typical effect of this mood stabilizer is the hypothyroidism, just as thyroid disease is more common in women.[20] Further, rapid –cycling bipolar illness, which some suggests more prevalent in women, is associated with thyroid abnormalities. However, other risk factors play an important role in the development of hypothyroidism, which include: first degree relative with hypothyroidism, elevated thyroid stimulating hormone (TSH) at baseline, weight gain, pre-existing antithyroid antibodies, iodine deficient diet, higher lithium levels and rapid cycling bipolar disorder. [20,68] Another adverse effect also associated with lithium therapy is the weight gain. Probably the women lifestyle, food intake or eating behavior might contribute to the occurrence of this reactions. [9]

Among the antipsychotics, clozapine, a second-generation antipsychotics (SGAs), emerges in the differential analysis of sex and ADRs. Most of the studies in the literature indicate that clozapine like olanzapine are associated with greater bodyweight gain than the other atypical antipsychotics.[69] This sex-related differences are likely to be a multifactorial phenomenon, although pharmacokinetics play an important role in the occurrence of ADRs. [63] Specifically, CYP1A2 is a major determinant for clozapine elimination with slight differences between men and women. Results suggest that women have higher plasma levels than men for clozapine and its metabolite norclozapine. [63] These sex specific differences are not detected for the metabolite N-oxideclozapine. Plasma levels of clozapine and N-desmethylclozapine may be affected by treatment duration.[63]

Prazepam is the only anxiolytic medication associated with female sex that we found in this research. Prazepam is a benzodiazepine derivative drug. It

possesses anxiolytic, anticonvulsant, sedative and skeletal muscle relaxant properties.[70]

To our knowledge, no available data about prazepam ADRs and the sex differences are published, as consequence our reflection regards the class of benzodiapines (BDZs). The growing realization that BDZs have potential for causing serious harm has caused concern due to their wide and common use. This has stimulated interest in the costs and benefits of their use. [15,30-32,71]

Data collected in the United States showed that, although many adverse effects have been documented, including the risk of increasing dosages to maintain the drug's effectiveness, benzodiazepines are still widely prescribed to reduce anxiety, insomnia, and agitation in individuals with severe mental illness.[72,73] BDZs are also believed to have fewer side effects, to be much safer in overdose, and to be much less liable to produce dependence and abuse problems.[71] However, these drugs are characterized by long-term side effects and physical/psychological dependence.[71,74] Despite the treatment recommendations stating that the benzodiazepine use should be short term, their pattern of use is often characterized by low-dose, long-term drug taking and low rates of discontinuation.[71,72,73,74] Another aspect to take into consideration is that concomitant psychotropic drug use was very frequent, and that absence of concomitant antipsychotics and mood stabilizers was a risk factor for long-term benzodiazepine use.[74] It seems therefore that benzodiazepines are used in addition to specific psychotropic drugs and/or when specific psychotropic drugs cannot be effectively employed.[37,74]

A group at special risk from adverse effects of BDZ is represented by elderly and by women. Elderly may be more likely to take BDZ several times a day, which increases the chance of psychomotor and memory function impairment and hip fractures, but they may also present with different symptoms of BDZ effects, particularly on withdrawal.[20,71,76]

Regarding the women, they represent the majority of patients who are prescribed benzodiazepines and are treated for benzodiazepine dependency. Despite that benzodiazepine induced sexual dimorphism on EEG, likely due to the different brain levels of neuroactive steroids, few studies evaluated the sex differences in therapeutic effects and side effects.[15,20] The preponderance of evidence suggests

that BDZs which are conjugatively metabolized have slower elimination rates in women than in men. [20] Oral contraceptives seem to inhibit clearance and decrease the rate of absorption. [20] As consequence, cognitive and psychomotor tasks were more impaired during the week off hormones in women taking oral contraceptives because BDZs peaked more quickly. This suggest that change in absorption rates for week off hormones led to a dose of BDZ which suddenly become intoxicating.[20,77]

In the analysis of the association with sex and the occurrence of ADRs, sertraline, a selective serotonin reuptake inhibitor (SSRI), is the only antidepressant strongly related to sex, specifically with male sex. Several SSRIs have been reported to exhibit significant gender-related differences in their pharmacokinetics.[21] Plasma concentration of sertraline was reported to be 50 to 100% higher in women and elderly men compared with young men, and gender-related CYP1A2 activity was proposed as one of the potential causes.[21,78]

Several studies have suggested that serotonin-related polymorphisms predict response of SSRI in patients with major depressive disorder.[21] Despite these findings, the clinical relevance of gender-related differences in pharmacokinetics remains unproven.[21,78]

3. Drugs analyzed in the "focus analysis"

In a separated analysis we deepened the research in relation to risperidone, alprazolam and paroxetine.

Risperidone, as well as almost of the second-generation antipsychotics (SGAs), may induced more frequent in female patients prolactin elevation, cardiac arrhythmia, called "*torsades de pointes*" (TdP), weight gain and type II diabetes.[7,62,63,69] The effect on the increased prolactin secretion may be explained by their blocking action on the lactotrophs and anterior pituitary gland type 2 dopamine (D2) receptors.[62] The women vulnerability to arrhythmia involved by risperidone might be due to the increased of sympathetic tone, such as occurs in acute psychotic states, the estrogens influence on bradycardia-induced prolongation of the QT interval, and to its capacity to block cardiac ion channels. [61,68]. Evidence suggests that the hormonal effects probably acts on (i) repolarisation of cardiac ion channels; (ii) expression levels of the ion channels; and (iii) the densities of the ion channels. [79] It is most likely that other factors such as gender-specific differences in intracellular and plasma drug levels might also play a role.[79] However, little is currently known regarding gender differences in the physiological response to sympathetic stimulation. [69]

Weight gain is another serious adverse effect of risperidone, as all SGAs, which increases the risk for developing a series of physical (e.g. diabetes) and psychological problems, but for women, extra weight also leads to reproductive problems and potential harm to the newborn. [62] The weight-gain liability of antipsychotic drugs has been attributed to histamine (H1) receptor binding, that affects feeding differently in the 2 sexes, and to their influence on both insulin and leptin levels. [62,69]

Alprazolam is a benzodiazepine derivative that is widely used in the treatment of generalized anxiety, panic attacks with or without agoraphobia, and depression. As was reported for BDZs, alprazolam may cause psychomotor effects, behavioral impairment as well as sedation, dependence, tolerance and withdrawal syndrome.[33,80] In particular symptoms of withdrawal from short-acting BDZs such as alprazolam are usually more severe to more rapid decreases in blood levels.[33] As was reported for prazepam, to our knowledge, few data exist on alprazolam sex differences in side effects. To understand the gender differences in

pharmacokinetics and pharmacodynamics, larger and specifically designed studies cannot be ruled out.[15]

Within antidepressants, paroxetine emerges from our data as the most prescribed and with a likely relation with side effects in women. Paroxetine is an SSRI antidepressants used to treat major depression, obsessive-compulsive, panic, social anxiety, and generalised anxiety disorders in adult outpatients. Extrapyramidal reactions, particularly dystonic reactions involving the face or mouth, appear to occur more frequently with paroxetine than with other serotonin reuptake inhibitors.[52] The extrapyramidal reactions (EPRs) occurred primarily in women (about 75%) possibly due to use of SSRIs for treating mental disorders common to women (i.e, depression). [52] Possible mechanisms by which SSRIs cause EPRs include: (1) central serotonergic activity which inhibits dopaminergic activity resulting in clinically significant effects; and (2) concurrent use of an SSRI and antipsychotic may cause EPRs by a pharmacokinetic interaction, a pharmacodynamic interaction, or a combination of the two. One of the most important evidence of the paroxetine use in women is its potentially teratogenicity effects during pregnancy.[52]

While some reports suggest that selective serotonin re-uptake inhibitors (SSRIs) are more effective and result in fewer adverse drug reactions in women than tricyclic antidepressants (TCAs), gender differences in antidepressant response remains a controversial topic.[81] The potential effects of antidepressant exposure in utero and in breast milk further complicate treatment options for antenatal and postnatal depression.[81]

In the “focus” analysis, we can observe that few patients take other drugs simultaneously with the psychotropic medications. However most of them are psychotropic drugs too. In the evaluation of the interaction between the suspected and the concomitant drugs, a potential drug-drug interactions (DDIs) was estimated for risperidone (suspected) with haloperidol (concomitant) or quetiapine (concomitant), alprazolam (suspected) with omeprazole (concomitant) or magnesium pidolate (concomitant), and paroxetine (suspected) with risperidone (concomitant).[52]

The adverse reactions, reported in reports where was find an interaction, describes aspects related to the effects reported in the literature for DDIs, although they are not identical.[52]

These data, although they relate to a small number of adverse reactions, show in some way, that there are difficulties in the proper management of psychotropic therapy, that leads to, or has the potential to lead to harm to the patient'.[82,83]

4. Limits

There are several limitations to our study that should be addressed. The primary limitation of this work is that no data is available about the drug utilization patterns of our patient population (i.e. prescription rates and types of medications). The exposure to drug, in fact, is fundamental to calculate the incidence of ADRs. In this analysis, it could not be determined whether there is an inherent increase in drug use among the female patients that would predispose them to experiencing a great number of adverse drug reactions.

However, we are currently collecting data on drug exposure in the 3 regions of France, Italy and Spain. Knowing the incidence of adverse drug reactions related to specific drugs or classes of drugs could help us to understand whether the differences reflect gender differences in drug consumption or gender differences in vulnerability to drug toxicity.[12]

In this study we did not present the distribution of drugs involved in the occurrence of ADRs by country. However, as the drug use, this analysis will be presented in a subsequent work.

Another limitation was that the ADR data were note studied in relationship to the incidence of diseases in the three regions according to gender.

Further, because this is a retrospective study, detailed information regarding specific adverse drug reactions was missing in some cases. Another possible bias is that women are more likely to have experienced of mental disorders, psychotropic drugs are more likely to be prescribed to females (and others to males) and that females live longer than males. In addition, the "gender bias" play an important role in the analysis of data. In fact the strongest limits derived from the fact that women are generally treated with doses that essentially reflect the results obtained by trials carried out mainly in men.[15]

Conclusion

The present study, which investigated the role of gender in ADRs reported to a regional French, Italian and Spain Pharmacovigilance centres, indicates that women are more prone than men to experience psychotropics induced adverse effects, especially when they are in the middle aged and take antidepressants. We found that adverse drug reactions derived from the lithium carbonate and prazepam assumption are more often associated with female sex, while from clozapine, and sertraline with male sex.

Few studies on this topic are available in the literature, the most of them are designed not to investigate differences between women and men. Further research should be performed to investigate the sex-specific drug safety of psychtropic use, taking into account potential risk factors, not only in relation to pharmacogenetics, pharmacokinetics and pharmacodynamics, but also in psychological, social, economic, political and cultural aspects.

Pubblication

The preliminary results of the first analysis of the data were presented in the poster session called “Pharmacoepidemiology, current controversies and opportunities” of the “WorldPharma” Congress 17-20th July, 2010, Copenhagen, Denmark. The abstract regarding this poster was published as follows: **Paola D’Incau**, M Lapeyre-Mestre, M Sa´inz, M Donati, A Carvajal. Gender differences of ADRs related to psychotropic drug use: a survey from France, Italy and Spain. Basic & Clinical Pharmacology & Toxicology. 2010; 107 (Suppl. 1): 162–692 (see Annex 3).

The preliminary results of the second analysis of the data were presented orally during the “II° National Congress on Gender Medicin e”, 21-23th October, 2010, Padua, Italy. The abstract entitled, “**Paola D’Incau**, M Lapeyre-Mestre, M Sa´inz, M Donati, A Carvajal, A. Conforti. Gender differences of ADRs related to psychotropic drug use: a survey from France, Italy and Spain”, was published in the official website of the European Society of Gender Health and Medicine: http://www.gendermedicine.org. (see Annex 3).

Acknowledgements

I would like to thank Dott. Anita Conforti (Department of Medicine and Public Health Section of Pharmacology University of Verona) and Prof. Maryse Lapeyre-Mestre (Service de Pharmacologie Clinique Faculté de Médecine, CEIP de Toulouse) for their support during the three years of doctorate.

I also thank: Prof. Alfonso Carvajal (Institute of Pharmacoepidemiology, University of Valladolid, Valladolid, Spain) for his collaboration in this study and all his staff (especially Ines Salado); Dott. Monia Donati (Department of Medicine and Public Health Section of Pharmacology University of Verona, Italy) for her important work on the Italian regional pharmacovigilance database; Dott. Laure Pourcel (Service de Pharmacologie Clinique Faculté de Médecine, CEIP de Toulouse) and Dott. Laura Bisoffi (Head of Biostatistics and Research Support Unit University of Verona) for their help with the statistics.

Finally, I thank the Prof. Maria Rosa Gaion (Department of Pharmacology, University of Padova) the head of the doctoral school and Prof. Giampaolo Velo (Department of Medicine and Public Health Section of Pharmacology University of Verona), the head of the Department of Medicine Section of Pharmacology of the University of Verona, the department in which I followed my research activities.

I thank also Prof. Roberto Leone, Dott. Ugo Moretti, Dott. Lara Magro, Dott. Riccardo Lora (Department of Medicine and Public Health Section of Pharmacology University of Verona) for their encouragement.

Funding

This project was self financed by the regional pharmacovigilance centres of Midi-Pyrénées, Veneto and Castilla-Leon.

References

1. WHO. International drug monitoring: the role of national centres. Tech Rep Ser WHO 1972, no 498.

2. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356:1255-1259.

3. Wiholm B.E., Olsson S., Moore N., Waller P. Spontaneous reporting systems outside the US, in: Strom B.L. (Ed.), Pharmacoepidemiology, 3rd edn, John Wiley & Sons, Chichester, UK. 2000, pp. 175–192.

4. Conforti A, Leone R, Ghiotto E, et al. Spontaneous reporting of drug-related hepatic reactions from two Italian regions (Lombardy and Veneto). Dig Liver Dis. 2000;32:716-723.

5. Edwards I, Olsson S: WHO: global monitoring. In Pharmacovigilance Edited by: Mann RD, Andrew E. Chichester: John Wiley & Sons. 2002:169-182.

6. Smith CC, Bennett PM, Pearce HM, et al. Adverse drug reaction in a hospital general medical unit meriting notification to the Committee on Safety of Medicines. Br J Clin Pharmacol. 1996;42:423-429.

7. Feely J, Moriarty S, O'Connor P: Stimulating reporting of adverse drug reaction by using a fee. Br Med J 1990;300:22-23.

8. Montastruc JL, Lapeyre-Mestre M, Bagheri H, Fooladi A. Gender differences in adverse drug reactions: analysis of spontaneous reports to a Regional Pharmacovigilance Centre in France. Fundam Clin Pharmacol. 2002;16:343-346.

9. Haack S, Seeringer A, Thürmann PA, et al. Sex-specific differences in side effects of psychotropic drugs: genes or gender? Pharmacogenomics. 2009;10:1511-2156.

10. Lazarou J, Pomeranz BH, Corey PN Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. JAMA. 1998; 279:1200–1205.

11. Davies EC, Green CF, Taylor S, et al. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One. 2009;4:e4439.

12. Martin RM, Biswas PN, Freemantle SN, et al. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. Br J Clin Pharmacol. 1998;46:505-511.

13. Tran C, Knowles SR, Liu BA, Shear NH. Gender differences in adverse drug reactions. J Clin Pharmacol. 1998;38:1003-1009.

14. Rademaker M. Do Women Have More Adverse Drug Reactions? Am J Clin Dermatol 2001; 2: 349-351

15. Franconi F, Brunelleschi S, Steardo L, Cuomo V. Gender differences in drug responses. Pharmacol Res. 2007;55:81-95.

16. Verdonk P, Benschop YW, de Haes HC, Lagro-Janssen TL. From gender bias to gender awareness in medical education. Adv Health Sci Educ Theory Pract. 2009 Mar;14:135-152

17. Zopf Y, Rabe C, Neubert A, et al. Women encounter ADRs more often than do men. Eur J Clin Pharmacol. 2008; 64:999–1004.

18. Payne J, Neutel I, Cho R, DesMeules M. Factors Associated with Women's Medication Use. BMC Womens Health. 2004; 25;4 Suppl 1:S29.

19. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. Annu Rev Pharmacol Toxicol. 2004;44:499-523.

20. Yonkers KA, Kando JC, Cole JO, Blumenthal S. Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. Am J Psychiatry. 1992 May;149:587-95.

21. Meibohm B, Beierle I, Derendorf H. How important are gender differences in pharmacokinetics? Clin Pharmacokinet. 2002;41:329-342.

22. Federman DD. The biology of human sex differences. N Engl J Med. 2006 Apr 6;354:1507-1514.

23. Franconi F., Montilla S., Vella S. Farmacologia di genere. Seed Editore. 2010 ISBN: 8889688513

24. Drici MD, Clément N. Is Gender a Risk Factor for Adverse Drug Reactions? The Example of Drug-Induced Long QT Syndrome. Drug Saf. 2001;24:575-585.

25. Needham B, Hill TD. Do gender differences in mental health contribute to gender differences in physical health? Soc Sci Med. 2010;71:1472-1479.

26. Cooperstock R. Psychotropic drug use among women. Can Med Assoc J. 1976;115:760-763.

27. World Health Organization. Improving Access and Use of Psychotropic Medicines. Full Report 2004. http://www.who.int/mental_health/policy/essentialpackage1/en/index1.html. Accessed November 17, 2010.

28. Kendler KS, Thornton LM, Prescott CA. Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. Am J Psychiatry. 2001;158:587-593.

29. Keita GP. Psychosocial and cultural contributions to depression in women: considerations for women midlife and beyond. J Manag Care Pharm. 2007;13:S12-S5.

30. Verdoux H, Tournier M, Bégaud B. Pharmacoepidemiology of psychotropic drugs: examples of current research challenges on major public health issues. Epidemiol Psichiatr Soc. 2009;18:107-113.

31. Alonso J, Angermeyer MC, Bernert S, et al. Psychotropic drug utilization in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl 2004; 55–64.

32. Barbui C, Percudani M. Epidemiological impact of antidepressant and antipsychotic drugs on the general population. Curr Opin Psychiatry. 2006;19:405-410.

33. Fankhauser MP. Psychiatric disorders in women: psychopharmacologic treatments. J Am Pharm Assoc (Wash). 1997;NS37:667-678.

34. Van der Heyden JH, Gisle L, Hesse E, et al. Gender differences in the use of anxiolytics and antidepressants: a population based study. Pharmacoepidemiol Drug Saf. 2009;18:1101-1110.

35. Dennerstein, L. Mental health, work, and gender. International Journal of Health Services: Planning, Administration, Evaluation.1995;25: 503-509.

36. Linzer M, Spitzer R, Kroenke K, et al. Gender, quality of life, and mental disorders in primary care: results from the PRIME-MD 1000 study. American Journal of Medicine. 1996;101:526-533.

37. D'Incau P., Barbui C., Tubini J., Conforti A. Stressful life events and social-health factors in women using anxiolytics and antidepressants. An Italian observational study in community pharmacies. Gender Medicine Journal. (Article in press)

38. Manninen BA. Medicating the mind: a Kantian analysis of overprescribing psychoactive drugs. J Med Ethics. 2006;32:100-105.

39. Hohmann AA. Gender Bias in Psychotropic Drug Prescribing in Primary Care. Medical Care. 1989;27: 478-490

40. Harman JS, Rollman BL, Hanusa BH, et al. Physician office visits of adults for anxiety disorders in the United States, 1985-1998. J Gen Intern Med. 2002;17:165-172.

41. Achille P. Caputi, Fabrizio De Ponti, Luigi Pagliaro. Reazioni avverse a farmaci. Sospetto e diagnosi. Milano: Raffaello Cortina Editore, 2009.

42. The National Institutes of Health (NIH). Mental Health Medications. 2010 http://www.nimh.nih.gov/health/publications/mental-health-medications/complete-index.shtml Accessed November 17, 2010.

43. Lapeyre-Mestre M, de Castro AM, Bareille MP, et al. Non-steroidal anti-inflammatory drug-related hepatic damage in France and Spain: analysis from national spontaneous reporting systems. Fundam Clin Pharmacol. 2006;20:391-395.

44. Leone R, Sottosanti L, Luisa Iorio M, et al. Drug-related deaths: an analysis of the Italian spontaneous reporting database. Drug Saf. 2008;31:703-713.

45. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2010. Available to www.whocc.no/filearchive/publications/2010guidelines.pdf. Accessed November 17, 2010.

46. International Nonproprietary Names [document on the Internet]. World Health Organisation. Available from: http://www.who.int/about/en/Uppsala Monitoring Centre (2008) Accessed November 17, 2010.

47. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–245

48. Be´gaud B, Evreux JC, Jouglard J, et al. Imputation of the unexpected or toxic effects of drugs: actualization of the method used in France. Therapie 1985; 40: 111-118

49. The Uppsala Monitoring Centre. Causality Assessment of Suspected Adverse Reactions, 2008. http://www.who-umc.org/DynPage.aspx?id=22682. Accessed November 17, 2010.

50. WHO Drug Dictionary. Available to http://www.who-umc.org/DynPage.aspx?id=13120&mn=m. Accessed November 17, 2010.

51. DRUGDEX® system [Internet database]. Greenwood Village (CO): ThomsonReuters (Healthcare) Inc., updated periodically.

52. van Puijenbroek EP, Bate A, Leufkens HGM, et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf. 2002; 11: 3-10

53. Camargo AL, Cardoso Ferreira MB, Heineck I. Adverse drug reactions: a cohort study in internal medicine units at a university hospital. Eur J Clin Pharmacol. 2006;62:143–149

54. Carbonin P, Pahor M, Bernabei R, Sgadari A. Is age an independent risk factor of adverse drug reactions in hospitalized medical patients? J Am Geriatr Soc. 1991;39:1093–1099

55. Hoigne R, Sollberger J, Zoppi M, et al. Significance of age, sex, kidney function, atopy and number of prescriptions for the occurrence of adverse drug reactions, studied by multivariate statistical methods. Results from the Comprehensive Hospital Drug Monitoring Berne (CHDMB). Schweiz Med Wochenschr. 1984;114:1854–1857.

56. van den Bemt PM, Egberts AC, Lenderink AW, et al. Risk factors for the development of adverse drug events in hospitalized patients. Pharm World Sci. 2000;22:62–66

57. Gray SL, Mahoney JE, Blough DK. Adverse drug events in elderly patients receiving home health services following hospital discharge. Ann Pharmacother. 1999;33:1147–1153

58. Zopf Y, Rabe C, Neubert A, et al. Gender-based differences in drug prescription: relation to adverse drug reactions. Pharmacology. 2009;84:333-339.

59. Johnell K, Weitoft GR, Fastbom J.Ann Pharmacother. Sex differences in inappropriate drug use: a register-based study of over 600,000 older people. 2009;43:1233-1238.

60. Bierman AS, Pugh MJ, Dhalla I, et al. Sex differences in inappropriate prescribing among elderly veterans. Am J Geriatr Pharmacother. 2007;5:147-161.

61. Uçok A, Gaebel W. Side effects of atypical antipsychotics: a brief overview. World Psychiatry. 2008;7:58-62.

62. Seeman MV. Secondary effects of antipsychotics: women at greater risk than men. Schizophr Bull. 2009;35:937-948.

63. W. Aichhorn, M. Gasser, E.M. Weiss, et al. Gender Differences in Pharmacokinetics and Side Effects of Second Generation Antipsychotic Drugs. Current Neuropharmacology. 2005; 3:73-85

64. Keers R, Aitchison KJ. Gender differences in antidepressant drug response. Int Rev Psychiatry. 2010;22:485-500.

65. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder (4th edn) (DSM–IV). APA, 1994

66. Tang NK, Salkovskis PM, Hodges A, et al. Effects of mood on pain responses and pain tolerance: an experimental study in chronic back pain patients. Pain. 2008;138:392–401.

67. Klauenberg S, Maier C, Assion HJ, et al. Depression and changed pain perception. Hints for a central disinhibition mechanism. Pain. 2008;140:332–343.

68. Elbe D, Savage R. J. How does this happen? Part I: mechanisms of adverse drug reactions associated with psychotropic medications. Can Acad Child Adolesc Psychiatry. 2010;19:40-45

69. Aichhorn W, Whitworth AB, Weiss EM, Marksteiner J. Second-generation antipsychotics: is there evidence for sex differences in pharmacokinetic and adverse effect profiles? Drug Saf. 2006;29:587-598.

70. Shader RI, Greenblatt DJ. "Benzodiazepines: some aspects of their clinical pharmacology". Ciba Found. Symp. 1979;74:141–155.

71. C. Gudex. Adverse effects of Benzodiazepines. Social Science & Medicine.1991; 33: 587-596.

72. Clark RE, Xie H, Brunette MF. Benzodiazepine prescription practices and substance abuse in persons with severe mental illness. J Clin Psychiatry. 2004;65:151–155

73. Brunette MF, Noordsy DL, Xie H, Drake RE. Benzodiazepine use and abuse among patients with severe mental illness and co-occurring substance use disorders. Psychiatr Serv. 2003;54:1395–1401.

74. Veronese A, Garatti M, Cipriani A, Barbui C. Benzodiazepine use in the real world of psychiatric practice: low-dose, long-term drug taking and low rates of treatment discontinuation. Eur J Clin Pharmacol. 2007;63:867-873.

75. National Institute for Health and Clinical Excellence, editor. Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. Full Report 2004. http://guidance.nice.org.uk/CG22. Accessed November 17, 2010.

76. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995;332:767-773.

77. Dawkins K, Potter WZ. Gender differences in pharmacokinetics and pharmacodynamics of psychotropics: focus on women. Psychopharmacol Bull. 1991;27:417-426.

78. Steiner M, Allgulander C, Ravindran A, et al. Gender differences in clinical presentation and response to sertraline treatment of generalized anxiety disorder. Hum Psychopharmacol. 2005;20:3-13.

79. Nicolson TJ, Mellor HR, Roberts RR. Gender differences in drug toxicity.Trends Pharmacol Sci. 2010;31:108-114.

80. Verster JC, Volkerts ER. Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: a review of the literature. CNS Drug Rev. 2004;10:45-76.

81. Uher R, Farmer A, Henigsberg N. et a. Adverse reactions to antidepressants. Br J Psychiatry. 2009;195:202-210.

82. Aronson JK. Medication errors: definitions and classification. Br J Clin Pharmacol. 2009;67:599-604.

83. Bencheikh RS, Benabdallah G. Medication errors: pharmacovigilance centres in detection and prevention. Br J Clin Pharmacol. 2009;67:687-690.

ANNEX 1.

The main results of this study were presented in the poster session called “Pharmacoepidemiology, current controversies and opportunities” of the “WorldPharma” Congress 17-20th July, 2010, Copenhagen, Denmark.

The abstract regarding this poster was published as follows: **Paola D’Incau**, M Lapeyre-Mestre, A Carvajal, U Bergman, ER Heerdink, RV Stichele, D Macias, L Pourcel, A Conforti. **A community pharmacy multinational project to Investigate the prescription drug abuse. Basic & Clinical Pharmacology & Toxicology**. 2010; 107 (Suppl. 1): 162–692

Prescription drug abuse and diversion have been reported as a critical concern in terms of patient care and public health, receiving conspicuously targeted consideration from health authorities. The aim of this article was to analyse the feasibility of carrying out the OSIAP system to detect the potential abuse of marketed drugs in a multinational community pharmacy setting.

An average of 2105 community pharmacies took part in the OSIAP project during 2006 and 2007. They reported a total of 862 suspect prescriptions concerning 1220 different drugs. The mean age of the total sample of subjects presenting suspect prescriptions was 45.12 years and the majority of them were women. The most frequently reported criteria of suspicion was "modification of the prescription” and most suspect prescriptions regarded the ATC N class. Of these drugs, 54% were psycholeptics (54% anxiolytics, 40% hypnotics and sedatives and 6% antipsychotics), 23% analgesics (72% opioids, 23% other analgesics and antipyretics and 5% antimigraine preparations) and 11% psychoanaleptics (66% antidepressants, 29% psychostimulants, 5% anti-dementia drugs and 1% psycholeptics and psychoanaleptics).

The OSIAP system provided useful information resulting from the patients’ everyday life, thus confirming potential role of a pharmacy network in limiting drug diversion. Further projects should be developed taking into consideration a variety of intervention strategies, from psychiatric intervention to practical law enforcement strategies. They should entail the collaboration of multidisciplinary efforts involving the abusers themselves in frontline educational activities.

Boeuf O & Lapeyre-Mestre M. Drug Safety 2007; 30: 265-276.

This article is under revision to be published Clinical Pharmacology & Therapeutics

A community pharmacy multinational project to investigate the prescription drug abuse

Authors' names: M Lapeyre-Mestre[1]; A Carvajal[2]; **P D'Incau[3]**; ER Heerdink[4]; RV Stichele[5]; D Macias[2]; A Conforti[3]; U Bergman[6]: OSIAP European Study

[1] Unit of Pharmacoepidemiology, Université Paul Sabatier, CEIP-A, Toulouse, France
[2] Institute of Pharmacoepidemiology, University of Valladolid, Valladolid, Spain
[3] Department of Community Medicine and Public Health, Section of Clinical Pharmacology Unit, University of Verona, Italy
[4] Department of Pharmacoepidemiology, University, Utrecht, Netherlands
[5] Dept of Pharmacology, Ghent University Hospital, Ghent, Belgium
[6] Karolinska Institute - Dept of Physiology & Pharmacology, Stockholm, Sweden

Keywords: drug abuse, suspect prescriptions, community pharmacy, Europe

ABSTRACT

Prescription drug abuse and diversion have been reported as a critical concern in terms of patient care and public health. The aim of this article was to analyse the feasibility of carrying out the OSIAP system to detect the potential abuse of marketed drugs in a multinational community pharmacy setting. An average of 2105 community pharmacies took part in the OSIAP project during 2006 and 2007. They reported a total of 862 suspect prescriptions concerning 1220 different drugs. The mean age of the total sample was 45.12 years and the majority of them were women. The most frequently reported criteria of suspicion was "modification of the prescription" and the most suspect prescriptions regarded the "Nervous system", primarily psycholeptics, analgesics and psychoanaleptics. The OSIAP system provided useful information resulting from the patients' everyday life, thus confirming the potential role of a pharmacy network in limiting drug diversion.

INTRODUCTION

Prescription drug abuse and diversion has been reported as a critical concern both, in terms of patient care and public health; consequently, it has received conspicuously targeted consideration from health authorities.[1-4]

Although much of the recent attention given to these topics has focused on experimental and clinical studies, the risk of prescription drug abuse in real life remains poorly characterized in the literature,[5] most of the data come from epidemiological studies conducted in the addict population. Nevertheless, drug abuse involves a significant part of the population who are not usually considered as addicts (e.g. long-term abusers of benzodiazepines who become dependent for years after prolonged time of exposure).[5] Considering the potential for misuse and inappropriate use of many psychiatric medications with sedative, anxiolytic, analgesic, or stimulant properties, linked to a number of serious adverse outcomes, [2] abuse is a chronic problem, with social, physical, and psychological harmful consequences. [6.] Among all types of drug diversion strategies, defined as "the unlawful channelling of regulated pharmaceuticals from legal sources to the illicit marketplace", theft, forgery, or alteration of prescriptions by patients may represent a significant proportion of cases of medication misuse.[1-5] As Kenneth *et al* reported, prescription medications are becoming the abused drugs of choice in economically developed countries.[4]

Within this context the community pharmacies opened to the public (private or public) are in a good position to contribute to limiting diversion and to support the medical system assistance to those who suffer from drug abuse problems. [6] Pharmacies are geographically well distributed, with the "front-line" role they play, easily accessible to, and regularly contacted by patients, offering an informal environment well placed to provide services for community-dwelling patients. [7] Following a state-of-the-art literature review on drug abuse and diversion through the PubMed database from January 1989 to November 2009, emerges that the programs of research carried out in pharmacies were mainly descriptive [8-17] without any patient intervention in the pharmacists' activities; focused on "over-the-counter" (OTC) [8,11,15,18] and methadone drug abuse [9,10,13,16,17]. Only few of them reported specific information on the potential for abuse of prescribed medicines. [18-22] To our knowledge, over the years, some research on pharmaceuticals drug abuse and diversion involving

pharmacies have been developed. However, the results obtained in these studies encourage developing pharmacist's program to provide drug misuse services which requires community pharmacists to work in concert with patients. Bergman *et al.* first, and Lapeyre-Mestre *et al.* then, described the principle of data collection concerning prescription forgery in the community pharmacy setting.[19,20] Their results suggest that forged prescriptions can be used as a "signalling mechanism" in epidemiological surveillance system of medication abuse and could be helped by community pharmacists research activities.
Following the results from the "OSIAP" program (*Ordonnances Suspectes Indicateur d'Abus Possible*, in French; Suspect Prescription Forms as an Index of Abuse Potential, in English), [5,20] an extended European version of this system about potential abuse liability of marketed drugs, was promoted in six countries (France), Belgium, Italy, Netherlands, Spain and Sweden).[23] OSIAP program was first developed to investigate and to systematize the identification, the collection and the analysis of suspect prescription forms, in order to validate a reproducible and reliable method for the assessment of the abuse potential of marketed drugs. In this paper we have focused on the feasibility of carrying out this system in a pharmacy setting at a multinational level, with a view to better understanding the differences in drug diversion strategies among the countries involved

RESULTS

Descriptive data

As shown in Table 1, 2105 community pharmacies took part in the OSIAP project; a total of 862 suspect prescriptions forms, concerning 1220 different drugs, was identified, - 418 prescriptions forms in 2006 (599 drugs) and 444 in 2007 (621 drugs). Most of the suspicions came from France (72% of all, accounting for 79% of all identified drugs). When considering the population cover for these pharmacies, the estimated suspect prescriptions forms was higher in Spain than in the other countries (see Table 1). Subjects presenting suspect prescriptions, had on average an age of 45 years (SD, 16.7), being the majority of subjects women (52%): a proportion of 56% of all subjects was known in person to pharmacists. A part from Italian population [SD, 38.67(11.06) years], the distribution of age was similar among the participating countries. Nevertheless, in Italy, Spain and Sweden, the male gender was well represented (by 50%, 57%, and 50 % of subjects, respectively), and only in Spain 71% of subjects were unknown to pharmacists.

Drug diversion data

Criteria of suspicion reported by pharmacists are listed in Table 2. The most frequently reported ones in all countries were "modification of the prescription" (46 %), followed by "not obeying prescription rules" (16 %), "writing over" (16%) and "addition of a drug" (15%). Nevertheless, this trend differed among countries: "copying and scanning" was the second more representative in Spain (28%), while the third in Belgium (19%) and the fourth in France (14%). "Abnormal prescribed dose" was the third more reported (30%) in Italy. Only in Sweden, all of the suspect prescriptions were collected throgh the "modification of the prescription" criterion (100 %).
Of all the 1220 different drugs identified, most of the suspect prescriptions (62%) regarded the "Nervous system" (Table 3). "Cardiovascular system" (8%), "Alimentary tract and metabolism" (8%) and "Respiratory system" (4%) were the other most frequent classes of suspect drugs.
The comparison by country indicates that cardiovascular drugs were identified only in France (98% of "Cardiovascular system"), whereas respiratory drugs were mainly identified in Belgium (6% of "Respiratory system"). Genito-urinary drugs and anti-infective drugs were mainly identified in Italy and in Spain: 2% and 21% of "Genito urinary system and sex hormones"; 5% and 16% of "Antineoplastic and immunomodulating agents", respectively.
Of the 758 "Nervous system" drugs reported through 604 suspect prescriptions (70% of the total), 54% was "psycholeptics" (of which 54% anxiolytics, 40% hypnotics and sedatives and 6% antipsychotics), 23% "analgesics" (of which 72% opioids, 23% other analgesics and antipyretics and 5% antimigraine preparations) and 11% "psychoanaleptics" (of which 66% antidepressants, 29% psychostimulants, 5% anti-dementia drugs and 1% psycholeptics and psychoanaleptics).
Zolpidem (10%), bromazepam (9%), alprazolam (9%), buprenorphine (7%), codeine and combinations (7%) were the main reported medications in all countries during the OSIAP survey in 2006-2007 (Table 4). However, this distribution differed by country, for example: flunitrazepam is at the 1th rank in Belgium, while zolpidem in France, lormetazepam in Italy, alprazolam in Spain and tramadol in Sweden are at the 1th rank.

Cluster analysis of the 10 most prescribed drugs

In the dendrogram (Figure 1) a selection of 17 clusters was reported. These clusters, also listed in Table 5, were sorted following the hierarchy of the most frequently diverted drugs. Zolpidem, at the 1st OSIAP rank, was present alone in the cluster number 3, described by the "coping/scanning" variable, and together alprazolam in cluster number 17, described by the "Spanish" country and the "abnormal prescribed dose" variables. Bromazepam, at the 2nd OSIAP rank, was reported in clusters number 11, 19 and 2. Two of them concerned known French subjects, of which only one reported the male gender. Following the list, alprazolam was reported cluster number 10, in which the data were significant only for Spanish population.
Buprenorphine was described in two clusters, number 7 and 4. Of the all variables, the age of diverting population under 35 years old was significant for each of these clusters. Nationality (i.e. France) and knowledge in cluster number 7, as well as male gender in cluster number 4 were also significant variables.
Codeine and its combinations (cluster n° 8) as well as tramadol (cluster n° 14) were reported only from Swedish diverted prescriptions, in which only the suspicion criteria represented a significant variable. Zopiclone (cluster numbers 9) was reported without any other significant variable. Population belonging to cluster number 1 diverted prescriptions for paracetamol and was referred to as French women, older than 55 years, and known to pharmacists.
Lorazepam and methylphenidate were reported in clusters number 5 and 16 regarding the Spanish subjects. In cluster number 5, they were known and older than 55 years, while in cluster number 16 they were unknown and younger than 55 years.
The subjects belonging to clusters number 12 and 6 diverted prescriptions for flunitrazepam and were from Belgium and France. Among these, gender and age were defined only in cluster number 6 the: men below 35 or 35-44 years old, respectively. Finally, oxazepam cluster number 15 was described only through the "spelling mistake" suspicion criteria variable.

DISCUSSION

The results of this study show that the diversion of prescription drugs does occur across different countries and might account for an important public health and safety issue. The comparative analysis of Belgium, France, Italy, Netherlands, Spain and Sweden data suggest anyhow that information on suspect prescriptions differ in quality and quantity. A possible explanation for these differences may come from the different type of community pharmacies networks. In fact, the number of pharmacies, the population covered and the organisation of their services differ among the participating countries. Belgium is the country with the major density of community pharmacies (500 per million inhabitants), followed by Spain (480 per million inhabitants), France (370 per million inhabitants), Italy (300 per million inhabitants), Netherlands (110 per million inhabitants) and Sweden (100 per million inhabitants). In addition, in France and in Sweden, OSIAP was performed at national level and there was already an ongoing process of identification/reporting of suspect prescriptions. [5,19] In the other countries, OSIAP was set up as a pilot study within a limited network of regional sentinel pharmacies. Furthermore, the number of medical doctors per 1 million inhabitants also differs among the participating countries; the highest density being in Spain (430 per million inhabitants), followed by Belgium (390 per million inhabitants), Italy (370 per million inhabitants), France (340 per million inhabitants), Sweden (300 per million inhabitants) and Netherlands (250 per million inhabitants).
These observations may help to understand the variation in data and explain why, for example, it was not possible to detect diverted prescriptions in Netherlands, or why the highest number of data was found in France. In Netherlands, OSIAP was actually conducted at regional level, and, furthermore, the density of both community pharmacies and general practitioners is low. Consequently, a narrow circle of health professionals makes it difficult for a subject to divert a prescription; in France, for instance, where there is a high number of both, community pharmacists and of general practitioners, it is easier to divert prescriptions In Sweden halfway between France and Netherlands, even though the project was at national level, there is as well a low density of community pharmacists and of general practitioners; in addition, there is a unique National Pharmacy Corporation (Apoteket).[19]
It is recognized that one of the reasons for the poor characterization and understanding of prescription medication misuse is the lack of universally-accepted standard criteria. [2] In this project, all participating pharmacists used the same type of form for monitoring the diverted prescriptions, allowing a common classification for diversion. Thus, in this manner, it was possible to ascertain

that the most frequent criteria of suspicion in each country was "modification of the prescription", the only way of diversion in Sweden, except in Spain which it was "not obeying prescription rules".
Through this strategy, the overall data analysis shows that the most diverted drugs belong to the "Nervous system" drug class, of which psycholeptics (anxiolytics, hypnotics - sedatives and antipsychotics) were more often reported than analgesics and psychoanaleptics. These data expand the drugs which are subjected of diversion since the attention given to these topics had focused on the non-medical use of prescription opioids.[1] The current literature suggests that approximately 0.4% of the world's population abuses at least one form of opioid and in Europe about 1.4 million (1.2-1.5 million) people abused opioids during the period 2002-07. [24,25]
On comparing "Nervous system" diverted drugs across countries, the differences of psycholeptics and psychoanaleptics trends indicate a partition between Nordic and South states. While in Sweden opioids (specifically tramadol) are almost exclusively diverted, in France, Italy, Spain and also in Belgium, anxiolytic and hypnotic benzodiazepines are the most reported drugs.
The overall analysis of OSIAP results is in line with research evidence, but, as Hamunen *et al.* highlighted, caution is required when interpreting the data between countries because there are differences in availability, marketing, reimbursement and prescription policies, as well as national and international guidelines for drug use, with the result of different drug consumption. [26,27]
Buprenorphine (at the 3rd OSIAP rank, diverted only in France), for example, although it has been scheduled at the III level of psychotropic drugs of the 1971 UN Single Convention on Psychiatric Substances for presenting a risk of abuse, and posing a serious threat to public health, is available in community pharmacies only in France. [23] Codeine (at the 4th OSIAP rank, diverted in France and in Sweden), as an internationally classified narcotic, is available in France in some specialities not subject to normal prescription rules, so freely available in community pharmacies, [18] and in Sweden, at least during OSIAP, it was not classified as narcotics but only as a drug with medicinal use and a risk of addiction. [23] Another drug to be highlighted is tramadol. It was essentially diverted in Sweden because only in this country, until September 2007, tramadol was not scheduled as a narcotic, and special prescription forms were not still required for this drug. [28,29] Epidemiological studies undertaken in the United States, investigating the abuse potential of tramadol in real-life settings have shown an overall low occurrence of tramadol abuse. [30] Cicero *et al.* [31] made several interesting reflections examining trends in the prescription abuse of tramadol. In particular, the fact that prescription drugs of all diversion strategies are relatively easily obtained, not monitored by law enforcement officials, their use/abuse is more socially acceptable, their purity and dosage are much safer to use than illicit drugs, and they can be useful as self-medications to relieve symptoms of heroin withdrawal or in an effort to detoxify. The questions of emerging security aspects of prescription diversion, although regarding the USA status, are somewhat transferred to OSIAP and, in general, to the European setting.
Of other diverted drugs that emerged from OSIAP project, dextropropoxyphen, withdrawn since 2005 in UK and Sweden, was diverted in France as it was the only country in which this narcotic was prescribed with a normal prescription form available for one year. In 2009 the European Medicine Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of all medicines containing dextropropoxyphene, either on its own or in combination, do not outweigh their risks, such as the risk of fatal overdose, therefore, the Committee has recommended that the marketing authorisations for these medicines be withdrawn across the EU [32].
Exploring drug diversion through cluster analysis, paracetamol in France and methylphenidate in Spain emerge among the significant diverted drugs in two of the 17 most representative clusters. Abuse and misuse of OTC analgesics associated with chronic pain, dysphoric mood states, sleep disturbances and so on are well known. [11,18,33] However, it is remarkable that a stimulant medication used in the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) has been identified as a diverted drug; this drug, although related to amphetamine, is not currently considered as a narcotic and it is available with a normal prescription form. [23]
It is worth noting that flunitrazepam (at the 9th OSIAP rank), in particular, but also other benziodiazepines were probably diverted due to their paradoxical reactions. Flunitrazepam is known to induce anterograde amnesia and it has been used to aid in the commission of sexual assault; it also has a calming and anti-emotive effect which allows criminals to commit robbery. [34,35]
Finally, among other benzodiazepines detected through this project, clonazepam, diazepam and tetrazepam, three potent anticonvulsants with anxiolytic properties, emerged probably for their unusual diverted use: clonazepam for its muscle relaxant and a sedative "off label" effects, [36] diazepam for its distressing effects in withdrawal symptoms and general discomfort, [37] tetrazepam, differently from flunitrazepam, for its drug-facilitated crime effect. [38] Tetrazepam may reduce the capacity of a victim to react against sexual assault, thus facilitating the criminals to commit acts of violence.

As with other studies carried out in the community pharmacy settings, [39] this study presents intrinsic limitations which may be due to not homogeneous samples among the participating countries . There were several barriers to achieve a similar amount in each participating country; among other reasons, it was because of the different legal, political and healthcare systems of these countries. Thus, since OSIAP study is based on regional data (from Belgium, Italy, Netherlands and Spain), they might not necessarily compare to the data collected in France and Sweden coming from the whole country. Other limitations of the present study may be related to a reflection recently raised by Strassels. [40] He underlined that "drug abuse can occur not only when a patient at risk for addiction is exposed to a certain drug, but also at any juncture when drugs are diverted to individuals for whom they are not medically intended". Although several drugs were found in diverted prescriptions even if they are not known for their addictive potential (drugs for acid related disorders, diuretics, lipid modifying agents, sex hormones and modulators of the genital system, urologicals, antibacterials for systemic use, antiinflammatory and antirheumatic products and muscle relaxants) further investigations are needed for understanding the difference and/or the correlation between prescription drug abuse and prescription drug misuse.
Despite all the limitations, OSIAP was a demonstration of the feasibility of monitoring prescription diversion in the community pharmacy setting at a multinational level. This system provided useful information resulting from the patients' everyday life, thus confirming the potential role of a pharmacy network in limiting the drug diversion. [6]
In order to avoid that "for many abusers prescription drugs serve as a first step or initial "gateway" to careers in substance abuse",[1] active monitoring and intervention programs aimed at addressing the problem of drug abuse will be increasingly required within multidisciplinary efforts. Further projects should be developed taking into consideration a variety of intervention strategies, from psychiatric intervention to practical law enforcement strategies. [6] They should entail the collaboration of health care providers, regulators, policy makers, addiction consultants, epidemiologists, pharmaceutical companies, and law enforcement, involving the abusers themselves in frontline educational activities.

METHODS

The Ordonnances Suspectes Indicateur d'Abus Possible (OSIAP) project was performed in three steps: the inventory, the implementation of community pharmacies networks and the data collection.

Inventory. The first step of the project was an inventory, a registry of all prescription medicines and their status in each country (for example, narcotic, psychotropic or any drug with a special rule of prescription and/or delivery).
This inventory excludes illicit drugs, which are prohibited in each participating country and medicinal products for which the only limitation is prior approval by health insurance systems. The list includes the following items for each medication: International Nonproprietary Names – INN [41]; classification code according to the 1961 and 1972 UN Conventions [42]; classification code according to the Anatomic Chemical Therapeutic Classification (ATC, see **Supplementary Table S1**); Defined Daily Dose (DDD).[43]

Community pharmacies networks. The second step was the constitution in each participating country of a network of community pharmacies for the collection of data concerning suspect prescription forms. These networks covered all the country (France, Sweden) or part of the country (Belgium, Italy, Netherlands, Spain).

Data collection. The third step was the data collection of suspect prescriptions. Several criteria were proposed and included in the data collection formulary sent to the pharmacies, in order to facilitate the identification and characterization of a suspect prescription form: unknown patient (important criterion of suspicion in Netherlands) and unknown prescriber; modification of the prescription (writing over or different writing); abnormal recommended dose or abnormal quantity or abnormal duration; prescription not in agreement with prescriptions rules (mentioned in the Summary Product Characteristics of drugs or specific rules for narcotic or psychotropic drugs); abnormal refilled request; spelling mistakes; copy the prescription form; stolen prescription form.

The pharmacist could identify one or more of these criteria, or any other observation which he would consider as relevant to suspect an alteration of the prescription form. Taking into account the difference between the 6 countries in developing the pharmacies networks, in this analysis we consider the data collected in 3 months (in spring and in fall-winter) of 2006 and 2007.

Statistical analysis

The first step was a descriptive analysis of OSIAP in each country including characteristics of persons (gender, age and known in person to pharmacists), drugs involved and criteria of suspicion. To compare the number of OSIAP in each country, we calculated a number of estimated suspect prescriptions with the participation rate, based on the number of community pharmacies per million inhabitants and the number of pharmacies which took part in the collection.
Secondly, we performed a multiple correspondence analysis (MCA) and a cluster analysis (CA with the ward's method) using gender, age, know in persons to pharmacists, criteria of suspicion, country and the 10 most cited drugs. [44,45,46] The MCA is an extension of simple correspondence analysis to more than two variables. This method studies the possible relation between variables and gives a graphic representation which allows to see the connection or opposition between the characteristic of persons or the characteristic of drugs. The aim of CA is to give typology or segmentation that is to say a distribution of persons into clusters. This method consists in optimizing a criterion aimed at merging persons into clusters which shall be at the same time as homogenous and as distinct as possible. MCA is particularly suited to explore individual data like in surveys but it is not always sufficient to give a satisfactory view of the entirety of data. Graphic representations provide only part of the information and they are too complex to be easily interpreted. CA allows to complete and to detail MCA. The complementarity of MCA and CA aids data comprehension and interpretation. MCA underlines combinations (proximity and dissimilarity) of population characteristics. After this, CA tries to synthesize these similarities or dissimilarities with a dendrogram which allows to select one or more typologies of this population.
To describe each cluster, we used a Chi-square test to compare the cluster with the rest of the population. The statistical analysis was performed with SAS® 9.1. statistical software.

ACKNOWLEDGMENTS

The authors wish to thank the following for developing the OSIAP (Ordonnances Suspectes Indicateur d'Abus et de Pharmacodependance) project at the national level:
Belgium: Vander Stichele R, Heymans Institute of Pharmacology, Faculty of Medicine, University of Ghen, Mehuys Pharmaceutical Care Unit, Faculty of Pharmacy, University of Ghent, De Schutter J, Van Den Bossche B, Pauwels, Bouffioux ML, National Pharmaceutical Inspectorate.
France: Nathalie Richard and Marie-Anne Courné, Department of Psychotropic Drug and Narcotics, French Medicine Agency. Dott.ssa Laure Pourcel (Service de Pharmacologie Clinique Faculté de Médecine, CEIP de Toulouse) for her help with the statistics.
Italy: The professional orders of pharmacists of the Verona and Vicenza provinces and Ferderfarma of Veneto Region.
Netherlands: Utrecht Department of Pharmacoepidemiology.
Spain: Carvajal A, Instituto de Farmacoepidemiología. Universidad de Valladolid (Spain)
Sweden: Bergmann U. and O. Dahl-Puustinen, Health Ministry and to Drug Medicine Agency.
The authors gratefully acknowledge all community pharmacists of each country who took part in the OSIAP project.

CONFLICT OF INTEREST

The authors have no conflicts of interest that are directly relevant to the content of this manuscript. This study was funded by the European Commission in 2003 - Strand 3: Health Determinants – Public Health Programme, no other sources of funding were used to assist in the preparation of this manuscript.

The authors confirm all patients and personal identifiers have been removed or disguised so the patient and persons described are not identifiable and cannot be identified through the details of the story.

REFERENCES

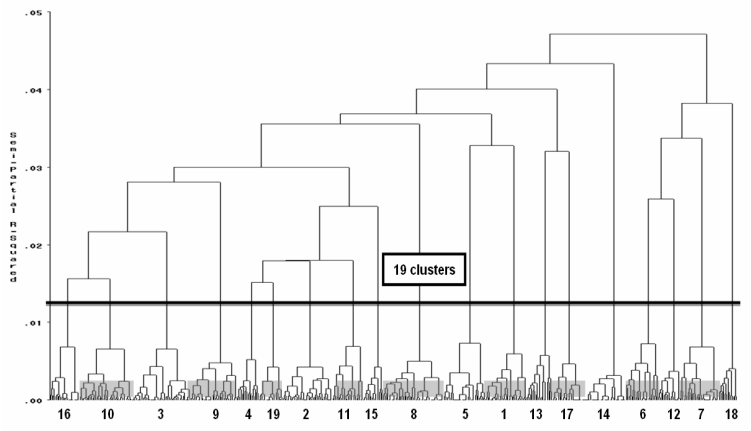
1. Inciardi, J.A., Surratt, H.L., Cicero, T.J. & Beard, R.A. Prescription Opioid Abuse and Diversion in an Urban Community: The Results of an Ultra- Rapid Assessment. *Pain Med*. April. **10**, 537–548 (2009).
2. Barrett, S.P., Meisner, J.R. & Stewart, S.H. What Constitutes Prescription Drug Misuse? Problems and Pitfalls of Current Conceptualizations. *Curr Drug Abuse Rev*. **1**, 255-262 (2008).
3. Inciardi, J.A., Surratt, H.L., Kurtz, S.P. & Cicero, T.J. Mechanisms of Prescription Drug Diversion Among Drug-Involved Club- and Street-Based Populations. *Pain Med*. April. **8**, 171-183 (2007).
4. Hale, K.M., Murawski, M.M. & Huerta, J. Pharmacist roles in combating prescription drug abuse. *J Am Pharm Assoc*. **49**, 589-592 (2009).
5. Boeuf, O. & Lapeyre-Mestre, M. Survey of forged prescriptions to investigate risk of psychoactive medications abuse in France: results of OSIAP survey. *Drug Saf.* **30**, 265-276 (2007).
6. Aneed, A. E., Alaghehbandan, R., Gladney, N., Collins, K., Macdonald D. & Fisch B. Prescription drug abuse and methods of diversion: The potential role of a pharmacy network. *Journal of Substance Use*. **14**:75-83 (2009).
7. Lambert, BL. Face and politeness in pharmacist-physician interaction. *Soc Sci Med*. **43**, 1189-1198 (1996).
8. Hughes, G.F, McElnay, J.C., Hughes, C.M. & McKenna P. Abuse/misuse of non-prescription drugs. *Pharm World Sci*. **21**: 251-5 (1999).
9. Matheson, C., Bond, C.M. & Hickey, F. Prescribing and dispensing for drug misusers in primary care: current practice in Scotland. *Fam Pract*. **16**:375-379 (1999).
10. Matheson, C., Bond, C.M, & Mollison, J. Attitudinal factors associated with community pharmacists' involvement in services for drug misusers. *Addiction*. **94**:1349-1359 (1999).
11. MacFadyen, L., Eadie, D. & McGowan, T. Community pharmacists' experience of over-the-counter medicine misuse in Scotland. *J R Soc Promot Health*. **121**:185-192 (2001).
12. McElnay, J.C., Hughes, C.M., Sheridan, J. & Strang, J. The role of the community pharmacist in drug abuse: a comparison of service provision between. *Pharm World Sci*. **23**:13-16 (2001).
13. Matheson, C., Bond, C.M. & Pitcairn, J. Community pharmacy services for drug misusers in Scotland: what difference does 5 years make?. *Addiction*. **97**:1405-1411 (2002).
14. Lawrie, T., Matheson, C., Bond, C.M. & Roberts, K. Pharmacy customers' views and experiences of using pharmacies which provide drug misuse services. *Drug Alcohol Rev*. **23**:195-202 (2004).
15. Wazaify, M., Hughes, C.M. & McElnay, J.C. The implementation of a harm minimisation model for the identification and treatment of over-the-counter drug misuse and abuse in community pharmacies in Northern. *Patient Educ Couns*. **64**:136-141 (2006).
16. Matheson, C., Bond, C.M. & Tinelli, M. Community pharmacy harm reduction services for drug misusers: national service delivery and professional attitude development over a decade in Scotland. *J Public Health (Oxf)*. **29**, 350-357 (2007).

17. Samitca, S., Huissoud, T., Jeannin, A. & Dubois-Arber, F. The role of pharmacies in the care of drug users: what has changed in ten years. The case of a Swiss region. *Eur Addict Res*. **13**:50-56 (2007).
18. Orriols, L., Gaillard, J., Lapeyre-Mestre, M. & Roussin, A. Evaluation of Abuse and Dependence on Drugs Used for Self-Medication A Pharmacoepidemiological Pilot Study Based on Community Pharmacies in France. *Drug Saf* **32**, 859-873 (2009).
19. Bergman, U. & Dahl-Puustinen, M.L. Use of prescription forgeries in a drug abuse surveillance network. *Eur J Clin Pharmacol*. **36**, 621-623 (1989).
20. Lapeyre-Mestre, M., Damase-Michel, C., Adams, P., Michaud, P. & Montastruc, J.L. Falsified or forged medical prescriptions as an indicator.
Eur J Clin Pharmacol **52**, 37-39 (1997).
21. Nielsen, S., Dietze, P., Dunlop, A., Muhleisen, P., Lee, N. & Taylor, D. Buprenorphine supply by community pharmacists in Victoria, Australia: perceptions, experiences and key issues identified. *Drug Alcohol Rev*. **26**, 143-51 (2007).
22. Wazaify, M., Hughes, C.M. & McElnay, J.C. The implementation of a harm minimisation model for the identification and treatment of over-the-counter drug misuse and abuse in community pharmacies in Northern Ireland. *Patient Educ Couns*. **64**,136-41 (2006).
23. Centre d'Evaluation et d'Information sur la Pharmacodépendance de Toulouse, Centre Hospitalier Universitaire de Toulouse. Final implementation report OSIAP (September 2004- June

2008) [document on the Internet]. European Health online [updated 2009 ; cited 2009 November 13]. Available from: http://ec.europa.eu/health/ph_projects/2003/action3/action3_2003_18_en.htm
24.World drug report 2008 [document on the Internet]. United Nations Drug Control Programme and the Centre for International Crime Prevention [cited 2009 November 13]. Available from: http://www.unodc.org
25. Annual report on the state of the drugs problem in Europe 2009 [document on the Internet]. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [cited 2009 November 13]. Available from: http://www.emcdda.europa.eu/index.cfm
26. Hamunen, K., Paakkari, P. & Kalso, E. Trends in opioid consumption in the Nordic countries 2002–2006. *Eur J Pain*, **13**, 954-962 (2009).
27. Hamunen, K., Laitinen-Parkkonen, P., Paakkari, P., Breivik, H., Gordh, T., Niels, N.H., & Kalso, Eija. What do different databases tell about the use of opioids in seven European countries in 2002? *Eur J Pain*, **12***,* 705-715 (2008).
28. 2008 NATIONAL REPORT (2007 data) TO THE EMCDDA by the Reitox National Focal Point [document on the Internet]. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [cited 2009 November 13]. Available from: http://www.emcdda.europa.eu/index.cfm
29. Medical Products Agency. Classification document. Dnr: 359:2007/ 26138. Sweden, 2007.
30. Cicero, T.J., Inciardi, J.A., Adams, E.H., Geller, A., Woody, G.E. & Muñoz, A.
Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic products: results of an abuse monitoring system, 1994-2004. *Pharmacoepidemiol Drug Saf*. **14**:851-859 (2005).
31. Cicero, T.J., Dart, R.C., Inciardi, J.A., Woody, G.E., Schnoll, S. & Muñoz, A. The development of a comprehensive risk-management program for prescription opioid analgesics: researched abuse, diversion and addiction-related surveillance (RADARS). *Pain Med*. **8**:157-170 (2007).
32. Questions and answers on the withdrawal of the marketing authorisations for medicines containing dextropropoxyphene. [document on the Internet]. The European European Medicines Agency [cited 2009 November 13]. Available from: http://www.ema.europa.eu/pdfs/human/referral/dextropropoxyphene/40106109en.pdf
33. Abbott, F. V. & Fraser, M I. Use and abuse of over-the-counter analgesic agents. *J Psychiatry Neurosci*. **23**: 13–34 (1998).
34. Michel, L. & Lang, J.P. Benzodiazepines and forensic aspects. *Encephale*. **29**:479-85 (2003).
35. Ricaurte, G.A. & McCann, U.D. Recognition and management of complications of new recreational drug use. *Lancet*. **365**:2137-2145 (2005).
36. Chouinard G. The search for new off-label indications for antidepressant, antianxiety, antipsychotic and anticonvulsant drugs. *J Psychiatry Neurosci*. **31**:168-76 (2006).
37. New Evidence On Addiction To Medicines Diazepam Has Effect On Nerve Cells In The Brain Reward System [document on the Internet]. Medical News Today. [August 2008, cited 2009 November 13]. Available from: http://www.medicalnewstoday.com/articles/119284.php
38. Concheiro, M., Villain, M., Bouchet, S., Ludes, B., López-Rivadulla, M. & Kintz, P.
Windows of detection of tetrazepam in urine, oral fluid, beard, and hair, with a special focus on drug-facilitated crimes. *Ther Drug Monit*. **27**:565-570 (2005).
39. Van Mil Foppe, J.W. & Shulz, M. A review of pharmaceutical care in community pharmacy in Europe. *Harvard Health Policy Rev*. **7**:155-168 (2006).
40. Strassels, S.A. Economic burden of prescription opioid misuse and abuse.J *Manag Care Pharm*. **15**:556-562 (2009).
41. International Nonproprietary Names [document on the Internet]. World Health Organisation [cited 2009 November 13]. Available from: http://www.who.int/about/en/
42. Narcotic drugs [document on the Internet]. International Narcotics Control Board (INCB) [cited 2009 November 13]. Available from: http://www.incb.org/incb/en/narcotic_drugs.html
43. About the ATC/DDD system [document on the Internet]. The WHO Collaborating Centre for Drug Statistics Methodology [cited 2009 November 13]. Available from: http://www.whocc.no/atcddd/
44. Lebart L., Morineau A., Piron M. Statistique exploratoire multidimensionnelle. 3rd edition. Paris: Dunod, 2000.
45. Saporta G. Probabilités analyses des données et statistique Paris: Editions TECHNIP, 1990.
46. Leroux-Scribe C. L'analyse des données. Edition Eutopstat, 2002.

FIGURES

Figure 1. Dendrogram of the CA with ward's method



TABLES

Table 1 Characteristics of community pharmacists, suspect prescriptions, suspect drugs reported by country

Country	Pharmacies which took part *		Participation rate**	Suspect prescriptions		Estimated suspect prescriptions **		Suspect drugs	
	(n = 2105)			(n = 862)		(n = 1452)		(n = 1220)	
	n°	%	n°	n°		n°	%	n°	%
Belgium	138	7	0,28	27	3	98	7	30	3
France	898	43	2,43	618	72	255	18	963	79
Italy	96	5	0,32	10	1	31	2	11	1
Netherlands	50	2	0,45	0	0	0	0	0	0
Spain	44	2	0,09	96	11	1055	73	103	8
Sweden	880	42	8,80	111	13	13	1	113	9

* Mean of the 3 collections
** Per million inhabitants

Table 2 Suspicion criteria identified reported by pharmacists in the OSIAP project by country*

	Total		Belgium		France		Italy		Spain		Sweden	
	n°	%	n°	%	n°	%	n°	%	n°	%	n°	%
Modification	399	46	11	41	260	42	5	50	12	13	**111**	**100**
Not obeying prescription rules	138	16	10	37	74	12	5	50	**49**	**51**	0	0
Writting over	134	16	0	0	133	22	1	10	0	0	0	0
Addition of a drug	133	15	1	4	130	21	2	20	0	0	0	0
Copying/scanning	123	14	5	19	90	15	1	10	27	28	0	0
Abnormal prescribed dose	71	8	2	7	50	8	3	30	16	17	0	0
Spelling mistake	45	5	2	7	37	6	0	0	6	6	0	0
Overlapping	39	5	0	0	39	6	0	0	0	0	0	0
Stolen form	29	3	0	0	27	4	0	0	2	2	0	0
Nonsense	25	3	2	7	23	4	0	0	0	0	0	0

* Sum of columns may exceed 100, since some prescriptions could include more than one criterion.

Table 3 Distribution of drugs reported in suspect prescriptions according to the ATC* classification by country

Anatomical group and therapeutic group*	Total (n = 1220)		Belgium (n = 30)		France (n = 963)		Italy (n = 11)		Spain (n = 103)		Sweden (n = 113)	
	n°	%	n°	%	n°	%	n°	%	n°	%	n°	%
Alimentary tract and metabolism	**98**	**8**	**1**	**3,3**	**91**	**9**	**1**	**9**	**2**	**2**	**3**	**3**
Stomatological preparations	3	0	0	0,0	3	0	0	0	0	0	0	0
Drugs for acid related disorders	31	3	1	3,3	28	3	0	0	1	1	1	1
Drugs for functional gastrointestinal disorders	20	2	0	0,0	19	2	1	9	0	0	0	0
Antiemetics and antinauseants	1	0	0	0,0	1	0	0	0	0	0	0	0
Laxatives	7	1	0	0,0	7	1	0	0	0	0	0	0
Antidiarrheals, intestinal antiinflammatory/antininfective agents	8	1	0	0,0	7	1	0	0	0	0	1	1
Antiobesity preparations, excl.diet products	3	0	0	0,0	2	0	0	0	1	1	0	0
Drugs used in diabetes	9	1	0	0,0	9	1	0	0	0	0	0	0
Vitamins	3	0	0	0,0	2	0	0	0	0	0	1	1
Mineral supplements	9	1	0	0,0	9	1	0	0	0	0	0	0
Other alimentary tract and metabolism products	4	0	0	0,0	4	0	0	0	0	0	0	0
Blood and blood forming organs	**14**	**1**	**0**	**0,0**	**14**	**1**	**0**	**0**	**0**	**0**	**0**	**0**
Antithrombotic agents	10	1	0	0,0	10	1	0	0	0	0	0	0
Antihemorrhagics	1	0	0	0,0	1	0	0	0	0	0	0	0
Antianemic preparations	3	0	0	0,0	3	0	0	0	0	0	0	0
Cardiovascular system	**103**	**8**	**0**	**0,0**	**101**	**10**	**0**	**0**	**2**	**2**	**0**	**0**
Cardiac therapy	4	0	0	0,0	4	0	0	0	0	0	0	0
Antihypertensives	2	0	0	0,0	2	0	0	0	0	0	0	0
Diuretics	24	2	0	0,0	23	2	0	0	1	1	0	0
Pheripheral vasodilators	3	0	0	0,0	3	0	0	0	0	0	0	0
Vasoprotectives	10	1	0	0,0	10	1	0	0	0	0	0	0
Beta blocking agents	11	1	0	0,0	11	1	0	0	0	0	0	0
Calcium channel blockers	8	1	0	0,0	8	1	0	0	0	0	0	0
Agents acting on the renin-angiotensin system	19	2	0	0,0	19	2	0	0	0	0	0	0
Lipid modifying agents	22	2	0	0,0	21	2	0	0	1	1	0	0
Dermatologicals	**29**	**2**	**0**	**0,0**	**29**	**3**	**0**	**0**	**0**	**0**	**0**	**0**
Antifungals for dermatological use	3	0	0	0,0	3	0	0	0	0	0	0	0

Emollients and protectives	3	0	0	0,0	3	0	0	0	0	0	0	0
Antipsoriatics	2	0	0	0,0	2	0	0	0	0	0	0	0
Corticosteroïds, dermatological preparations	11	1	0	0,0	11	1	0	0	0	0	0	0
Antiseptics and disinfectants	6	0	0	0,0	6	1	0	0	0	0	0	0
Anti-acne preparations	4	0	0	0,0	4	0	0	0	0	0	0	0
Genito urinary system and sex hormones	**43**	**4**	**1**	**3,3**	**31**	**3**	**1**	**9**	**9**	**9**	**1**	**1**
Gynecological antiinfectives and antiseptics	2	0	0	0,0	2	0	0	0	0	0	0	0
Other gynecologicals	1	0	0	0,0	0	0	0	0	1	1	0	0
Sex hormones and modulators of the genital system	22	2	1	3,3	19	2	0	0	2	2	0	0
Urologicals	18	1	0	0,0	10	1	1	9	6	6	1	1
Systemic hormonal preparations	**14**	**1**	**1**	**3,3**	**13**	**1**	**0**	**0**	**0**	**0**	**0**	**0**
Pituitary and hypothalamic hormones and analogues	1	0	0	0,0	1	0	0	0	0	0	0	0
Corticosteroids for systemic use	3	0	1	3,3	2	0	0	0	0	0	0	0
Thyroid therapy	10	1	0	0,0	10	1	0	0	0	0	0	0
Anti-infectives for systemic use	**19**	**2**	**1**	**3,3**	**14**	**1**	**1**	**9**	**3**	**3**	**0**	**0**
Antibacterials for systemic use	16	1	1	3,3	11	1	1	9	3	3	0	0
Antivirals for systemic use	1	0	0	0,0	1	0	0	0	0	0	0	0
Vaccines	2	0	0	0,0	2	0	0	0	0	0	0	0
Antineoplastic and immunomodulating agents	**1**	**0**	**0**	**0,0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Endocrine therapy	1	0	0	0,0	1	0	0	0	0	0	0	0
Musculo-skeletal system	**69**	**6**	**1**	**3,3**	**55**	**6**	**0**	**0**	**4**	**4**	**9**	**8**
Antiinflammatory and antirheumatic products	30	2	1	3,3	26	3	0	0	2	2	1	1
Topical products for joint and muscular pain	8	1	0	0,0	8	1	0	0	0	0	0	0
Muscle relaxants	21	2	0	0,0	12	1	0	0	1	1	8	7
Antigout preparations	2	0	0	0,0	1	0	0	0	1	1	0	0
Drugs for treatment of bone diseases	8	1	0	0,0	8	1	0	0	0	0	0	0
Nervous system	**758**	**62**	**21**	**70,0**	**550**	**57**	**8**	**73**	**82**	**80**	**97**	**86**
Anesthetics	2	0	0	0,0	2	0	0	0	0	0	0	0
Anesthetics, local	2	0	0	0,0	2	0	0	0	0	0	0	0
Analgesics	**173**	**14**	1	3,3	113	12	1	9	5	5	53	47
Antiepileptics	24	2	0	0,0	22	2	0	0	1	1	1	1
Psycholeptics	**412**	**34**	15	50,0	294	31	7	64	55	53	41	36

Psychoanaleptics	**87**	**7**	4	13,3	60	6	0	0	21	20	2	2
Other nervous system drugs	56	5	0	0,0	56	6	0	0	0	0	0	0
Antiparasitic products, insecticides and repellents	**1**	**0**	**0**	**0,0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Antithelmintics	1	0	0	0,0	1	0	0	0	0	0	0	0
Respiratory system	**49**	**4**	**3**	**10,0**	**43**	**4**	**0**	**0**	**0**	**0**	**3**	**3**
Nasal preparations	11	1	0	0,0	10	1	0	0	0	0	1	1
Drugs for obstructuve airway diseases	18	1	0	0,0	18	2	0	0	0	0	0	0
Cough and cold preparations	9	1	3	10,0	4	0	0	0	0	0	2	2
Antihistamines for sytemic use	10	1	0	0,0	10	1	0	0	0	0	0	0
Other respiratory system products	1	0	0	0,0	1	0	0	0	0	0	0	0
Sensory organs	**14**	**1**	**0**	**0,0**	**13**	**1**	**0**	**0**	**1**	**1**	**0**	**0**
Ophthalmologicals	13	1	0	0,0	12	1	0	0	1	1	0	0
Otologicals	1	0	0	0,0	1	0	0	0	0	0	0	0
Various	**1**	**0**	**1**	**3,3**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
All other therapeutic products	1	0	1	3,3	0	0	0	0	0	0	0	0
No ATC code	**7**	**1**	**0**	**0,0**	**7**	**1**	**0**	**0**	**0**	**0**	**0**	**0**

* See **Supplementary Table S1** for further clarification

Table 4 List of drugs most frequently reported in suspect prescriptions by country

INN*	Total (n = 676)		Belgium (n = 19)		France (n = 498)		Italy (n = 7)		Spain (n = 66)		Sweden (n = 86)	
	n°	%	n°	%	n°	%	n°	%	n°	%	n°	%
Zolpidem	**68**	**10**	0	0,00	**58**	**11,65**	0	0,00	1	1,52	9	10,47
Bromazepam	**60**	**9**	4	21,05	54	10,84	0	0,00	2	3,03	0	0,00
Alprazolam	**60**	**9**	3	15,79	31	6,22	1	14,29	**18**	**27,27**	7	8,14
Buprenorphine	**49**	**7**	0	0,00	49	9,84	0	0,00	0	0,00	0	0,00
Codeine, combinations	**45**	**7**	0	0,00	28	5,62	0	0,00	0	0,00	17	19,77
Zopiclone	42	6	0	0,00	33	6,63	0	0,00	1	1,52	8	9,30
Paracetamol	33	5	0	0,00	32	6,43	0	0,00	0	0,00	1	1,16
Tramadol	31	5	0	0,00	2	0,40	0	0,00	0	0,00	**29**	**33,72**
Lorazepam	31	5	3	15,79	15	3,01	**3**	**42,86**	10	15,15	0	0,00

Methylphenidate	25	4	2	10,53	6	1,20	0	0,00	17	25,76	0	0,00
Flunitrazepam	24	4	**5**	**26,32**	18	3,61	0	0,00	0	0,00	1	1,16
Oxazepam	21	3	0	0,00	15	3,01	0	0,00	0	0,00	6	6,98
Potassium clorazepate	20	3	0	0,00	14	2,81	0	0,00	6	9,09	0	0,00
Lormetazepam	16	2	0	0,00	9	1,81	2	28,57	5	7,58	0	0,00
Clonazepam	15	2	0	0,00	14	2,81	0	0,00	0	0,00	1	1,16
Dextropropoxyphene	14	2	0	0,00	14	2,81	0	0,00	0	0,00	0	0,00
Furosemide	12	2	0	0,00	12	2,41	0	0,00	0	0,00	0	0,00
Morphine	12	2	0	0,00	10	2,01	0	0,00	1	1,52	1	1,16
Diazepam	12	2	0	0,00	2	0,40	1	14,29	3	4,55	6	6,98
Tetrazepam	11	2	0	0,00	10	2,01	0	0,00	1	1,52	0	0,00
Ibuprofen	10	1	1	5,26	9	1,81	0	0,00	0	0,00	0	0,00
Levothyroxine sodium	9	1	0	0,00	9	1,81	0	0,00	0	0,00	0	0,00
Paroxetine	9	1	1	5,26	8	1,61	0	0,00	0	0,00	0	0,00
Venlafaxine	9	1	0	0,00	9	1,81	0	0,00	0	0,00	0	0,00
Benfluorex	8	1	0	0,00	8	1,61	0	0,00	0	0,00	0	0,00
Fluoxetine	8	1	0	0,00	7	1,41	0	0,00	1	1,52	0	0,00
Tianeptine	8	1	0	0,00	8	1,61	0	0,00	0	0,00	0	0,00
Betamethasone	7	1	0	0,00	7	1,41	0	0,00	0	0,00	0	0,00
Cyamemazine	7	1	0	0,00	7	1,41	0	0,00	0	0,00	0	0,00

* INN = International Nonproprietary Names

Table 5 Distribution of national Daily Defined Doses (DDDs) per 1000 inhabitants per die in 2007 according to the first level of ATC classification[43]

Table 6. Characteristics of the 17 largest clusters containing the 10 most cited drugs*

Cluster	N drugs	Top 10	Sex	Age	Know patient	Country	Suspicion criteria
3	42	Zolpidem	—	—	—	—	Copying/scanning
17	21	Zolpidem + Alprazolam	—	—	—	Spain	Abnormal prescribed dose
11	22	Bromazepam	Men	—	Know	France	Modification + Writting over
19	15	Bromazepam	Men	—	Unknow	—	Spelling mistake + Copying/scanning
2	35	Bromazepam	—	—	Know	France	Copying/scanning
10	37	Alprazolam	—	—	—	Spain	Copying/scanning
7	27	Buprenorphine	—	< 35	Know	France	Overlapping
4	17	Buprenorphine	Men	< 35	—	—	Writting over
8	43	Codeine, combinations	—	—	Know patient missing	Sweden	Modification
9	33	Zopiclone	—	—	—	—	—
1	30	Paracetamol	Women	≥ 55	Know	France	Modification + Addition of a drug + Writting over
14	31	Tramadol	—	—	Know patient missing	Sweden	Modification
5	29	Lorazepam	—	≥ 55	Know	Spain	—
16	21	Methylphenidate	—	35-44 + 45-54	Unknow	Spain	Not obeying prescription rules
12	16	Flunitrazepam	—	—	—	Belgium	Abnormal prescribed dose + Not obeying prescription rules
6	23	Flunitrazepam	Men	< 35 + 35-44	—**	France	Spelling mistake + Stolen form
15	14	Oxazepam	—	—	—	—	Spelling mistake

* All variables in the table have p< 0.05
** Not significant data

ANNEX 2.

The main results of this study were presented in the poster session of the "International Margherita von Brentano Summerschool", 19-24th September, 2010, Berlin, Germany.

The following abstract regards the poster presented:

Paola D'Incau, Corrado Barbui, Anita Conforti. **The occurrence of stressful life events in women and the use of anxiolytics and antidepressants**. An observational study in community pharmacies.

Background. Several studies have demonstrated that women show both a heightened stress sensitivity and an increased proneness to emotional disorders, which may lead to high use of psychotropic drugs.

Aim. The purpose of this study was to expand the knowledge about the occurrence of stressful life events in the use of anxiolytic and antidepressant drugs in women.

Methods. Women (n = 11,357) attending 100 community pharmacies in the Italian Veneto Region were surveyed by pharmacists with regard to a number of general pharmacological features. Women independently filled in a written self-assessment questionnaire focused on stressful life events. Unconditional logistic regression was used to investigate the association between anxiolytic and antidepressant use and all potential factors including stressful life events.

Results. One or more stressful life events occurred in 90% of the women treated with anxiolytics and/or antidepressants (users) and in 74% of the women not treated with these drugs (nonusers) (OR = 3.19; 95% CI = 2.83-3.60). On average, the life events occurred during the previous 6 months and women considered their influence on their well-being as severe. After the unconditional logistic regression analysis, the association between anxiolytics and/or antidepressants use remained positive for the most stressful life events studied, and for the following other factors: separation/divorce, living alone, living with family or friends, unemployment, currently seen by a psychologist/psychiatrist, alimentary tract and metabolism, cardiovascular and nervous system drugs.

Conclusions. A significant association between stressful life events and anxiolytics and/or antidepressants use was observed. Further efforts are needed to increase the knowledge about the use of anxiolytics/antidepressants in relation to the occurrence of life events.

This article is press to Gender Medicine Journal

Title: Stressful life events and social-health factors in women using anxiolytics and antidepressants. An Italian observational study in community pharmacies.

Authors' names: **Paola D'Incau**, Corrado Barbui, Jacopo Tubini, Anita Conforti

ABSTRACT

Objective: The purpose of this study was to expand knowledge of how the occurrance of stressful life events in women was related to exposure/non exposure to anxiolytics and antidepressents in the Veneto Region of Italy. .

Methods: Women (n = 11357) attending 100 community pharmacies in the Italian Veneto Region were surveyed by pharmacists with regard to a number of general features of their current pharmacological treatment. Women independently filled in a written self-assessment questionnaire focused on stressful life events. Unconditional logistic regression was used to investigate the association between anxiolytics and antidepressants use and potential factors including stressful life events.

Results: One or more stressful life events occurred in 90% of the women treated with anxiolytics and/or antidepressants (users) and in 74% of the women not treated with these drugs (nonusers) (OR = 3.19; 95% CI = 2.83-3.60). On average, the life events occurred during the previous 6 months and women considered their influence on their well-being as severe. After the unconditional logistic regression analysis, the association between anxiolytics and/or antidepressants use remained positive for the most stressful life events studied, and for the following other factors: separation/divorce, living alone/with family/with friends, unemployment, currently seen by a psychologist/psychiatrist, alimentary tract and metabolism, cardiovascular and nervous system drugs.

Conclusions: A significant association between stressful life events and anxiolytics and/or antidepressants use was observed. Further efforts are needed to increase the knowledge about the use of anxiolytics/antidepressants in relation to the occurrence of life events.

Keywords: anxiolytics, antidepressants, life events, women, pharmacist

INTRODUCTION

In light of the current awareness, the women mental and physical health states associated with the exposure to stressful life events and social/personal factors are of considerable interest in health research today.[1,2]Several studies have demonstrated that women are a socially disadvantaged group. In Europe, female gender is a predictor of lower status, lower participation in decision-making and lower pay.[3]
Women are also disadvantaged as a result of the multiple roles they perform in society - worker, mother, partner, etc. - and, at the same time, of the expectations that our society associate with the general gender roles.[4] Women are more likely to have experienced poverty and discrimination and are more often victims of physical and sexual abuse. Women more often than men complain with housing problems, loss of a confidant, close relationship problems, and illness of individuals in the broader sphere of relatives and friends as stressful life events.[5]
It is possible that the greater impact of network events on women than in men is linked to the fact that women provide more support than men and that this creates stresses and demands that can lead to psychological impairment. As women might be more emphatic than men, they are may be related to the greater importance to the quality of interpersonal relations to those in their social networks.[1,6] The effect of the exposure to stressful life events may cause distress reactions that trigger psychological, biological, behavioral, and attentional mechanisms that precede the onset of depressive and anxiety disorders and, as a consequence, may lead to high use of psychotropic drugs.[7,8] According to the national statistics, emotional disorders, such as depression and anxiety, are increasing and spreading. These disorders are more frequent among women than men and occur to a greater extent with the increase of age.[9] In Italy central nervous system (CNS) drugs are in the third position for both expenditure and consumption of which the selective serotonin reuptake inhibitors (SSRIs) antidepressants are on the top.[10] The prevalence of use of CNS drugs is different between men and women, 27% and 36% respectively.[10] This Italian trend is also similar in the Veneto Region, where the study was conducted.
Given the extent of mental illness in the community and the rapid increase in prescribing psychotropic medications, services directed toward optimising the use of medications for mental illness fulfil an important public health need.[11,12] Although pharmacists have the potential to improve health outcomes for people with emotional disorders, only a limited number of investigations included pharmacists in research activities.[13] The majority of these studies have been descriptive, qualitative in nature and involved a few number of pharmacists and a few number of patients.[14, 15] To our knowledge, none of these have been developed in Italy.
The overall aim of the present study was to expand the knowledge about the occurrence of stressful life events in the women's use of anxiolytics and antidepressants in a community pharmacy setting. Specific aims were:

- to compare the frequency and the impact of stressful life events in women who use anxiolytics and antidepressants with women who do not use these drugs;
- to describe the pattern of anxiolytics and antidepressants use;
- to asses the association between use of anxiolytics and/or antidepressants and potential factors including stressful life events, social-demographics and health factors.

METHODS

Setting

This observational study was carried out in 8% (n = 100) of the Veneto community pharmacies (n total = 1316) open to the public by the 13% (n = 249) of the Veneto community pharmacists (n total = 1954) admitted to practice pharmacists' profession.[16] This research was developed within a continuing pharmacist education program focused on psycho-physical health of women.[17]
All Veneto community pharmacists were invited by email given by the Professional Associations and Association of Owners of Italian Pharmacies -Federfarma to participate. Of these, the 249 participating community pharmacists expressed an interest in being involved and agreed to take part voluntarily in the project.
Data were collected in the months of May and October as the changing of seasons might exacerbate the psychological and mental health malaise. This has been specifically reported for the seasonal affective disorders (SAD).[18]

Study population
The women were divided in two groups: anxiolytics and/or antidepressants users and anxiolytics and/or antidepressants nonusers. Women were considered users if they attended the pharmacy with a personal medical prescription for any anxiolytics and/or antidepressants. Women were considered nonusers if they attended the pharmacy for any other products and were not receiving any treatment with anxiolytics and/or antidepressants. Women were excluded from the study if they were younger than 18 years and if they did not sign the informed consent. Each user was matched by age (± 5 years) with two nonusers.

Study design
Each community pharmacist was asked to recruit one user and two nonusers per day for each month of the investigation. This strategy consisted in including as user the third woman who attended the pharmacy during each working day per week. These women were eligible if they met the inclusion criteria and signed the informed consent. The two consecutive women followed by the pharmacist who were not receiving any treatment with anxiolytics and/or antidepressants were selected as nonusers. The nonusers women were included in the study if they signed the informed consent.
Using a written questionnaire, pharmacists surveyed at the time of recruitment women who agreed to be involved in the project with regard to a number of general pharmacological features. The women then independently filled in a written self-assessment questionnaire. All participating women subsequently received a letter of gratitude from the pharmacist in which the telephone number of the Equal Opportunities Commission call centre was supplied. This was a way of supporting the women's potential "unexpressed" social needs.

Instruments
The research instruments adopted in the study consisted of two questionnaires: a questionnaire administrated and filled in by the pharmacists ("Pharmacist's questionnaire") and a questionnaire self-completed by the selected women ("Women's questionnaire"). These two questionnaires were identical for user and nonusers and were assigned an anonymous code number.
Pharmacist's questionnaire
This questionnaire was divided into two sections: one dedicated only to users and the other both to users and nonusers. The first section dealt with antidepressant and anxiolytic therapy: type of molecule classified according to the Italian drug classification;[10] duration of therapy (first usage, for 1-6 months, over 6 months); women's drug satisfaction (yes/no).
The second section included: a list of all prescribed drugs classified by the Anatomical Therapeutic Chemical Classification System (ATC) for Human Medicine;[17] if women use other drugs and herbal remedies and/or homeopathic products.
Specifically, the ATC classification system divided active substances into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Drugs are classified in groups at five different levels. For statistical analysis, the first ATC code was used.
Women's questionnaire
This questionnaire consisted in a series of items concerning social-demographics variables (i.e. provenance area, marital status, cohabitation, employment); health factors (i.e. ability to perform normal daily activities, currently seen by a psychologist/psychiatrist, currently seen by a social worker) and included a modified version of the List of Threatening Experiences (LTE).[18] This list identified 12 stressful "life events", critical life experiences carrying significant long-term threat or unpleasantness and capable of significantly influencing future episodes of depression.[19] The version used in this study deepened on the events regarding personal and relative assault differentiating in violent act outside the family and/or in the family. We additionally added 3 items derived from the Interview for Recent Life Events (IRLE) (i.e. "major close relative illness or injury", "miscarriage or abortion", "trouble at work"),[20] and one final item called "Other". On the whole, 19 items were included in the life events schedule.
According to the LTE, for each event the women were asked to tick the box or boxes corresponding to the month or months in which any event happened or began in the 6 months preceding the interview and to indicate the subjective level of influence on well-being, with the ratings "severe", "somewhat", "slightly" and "not at all".
A first version of the "Women's questionnaire" and the "Pharmacist's questionnaire" was piloted in a group of pharmacists not participating in the main study. The content and the face validity were discussed with experts of the Professional Associations and Association of Owners of Veneto

Pharmacies (Federfarma). The first version of the piloted questionnaires were agreed by the experts without any change and were adopted in the current study.

Ethics
According to Italian law, the study did not require approval by an ethics committee as the methodology was in accordance with Italian regulations concerning research activities developed within the framework of a continuing pharmacist education (CPE) program.
We also confirm all patients and personal identifiers have been removed or disguised so the patient and persons described are not identifiable and cannot be identified through the details of the story.

Analysis
Descriptive statistics for all variables were performed with Microsoft Excel 2000.
In the analysis, women selected as users were compared with nonusers regarding the occurrence of serious life events and demographics/social aspects, respectively, by calculating an unadjusted odds ratio (OR) with 95% confidence interval (CI).
Unconditional logistic regression was used to estimate the relative magnitude of the association between the risk for use anxiolytics and/or antidepressants and all the potential factors (social-demographics variables and health factors and the list of stressful life events), expressed as odds ratio (OR) and their 95 % confidence intervals (CI). Two tailed $p<0.05$ was considered significant.
After a bivariate analysis, the simultaneous effect of all the potential factors was then explored using a backward selection of the variables. All the analyses were performed with Epi-Info software (3.5.1 version).

RESULTS

Characteristics of the study population
During the study the participating pharmacists recruited 11475 women, the 4.6 ‰ of the total women inhabitants (n = 2464895) of Veneto Region (source ISTAT - National Institute of Statistics -2008). Of these 118 were not included in the analysis as they failed to match up to the selection criteria, with the result that the final analysis sample consisted of 11357 women. These women population consisted of 34% users (n = 3848) and 66% nonusers (n = 7509).
On analysing the demographic data for the total sample of users and nonusers, as shown in **Table I**, 33% of all these women were aged 50-64 years and also 33% were aged 35-49 years, while 21% were over 65 years old and 12% were under 35 years old. Sixty-six percent came from urban areas and 34% from rural areas.

Frequency and impact of stressful life events
One or more life events had occurred in 90% of the user and in 74% of the nonusers (OR = 3.19; 95% CI = 2.83-3.60). **Table II** shows the frequency of stressful life events in users and nonusers. Of the 19 life events the most frequent both in users and in nonusers were “close relative death” and “major close relative illness or injury”.
Apart from “close relative was a victim of a violent act out of family” (OR = 0,99; 95% CI = 0.69–1.41), “other relative death” (OR = 0.98; 95% CI = 0.89-1.08), “miscarriage or abortion” (OR = 1.11; 95% CI = (0.95-1.29) and “lost something important” (OR = 0.90; 95% CI = 0.78-1.05), all the unadjusted odds ratio values showed an association between the occurrence of life events and the use of anxiolytics and/or antidepressants.
On average, the life events occurred during the previous 6 months and women considered their influence on their well-being as severe. The self-rated level of influence was esteemed as severe in 69% of users and 55% of nonusers, somewhat in 25% of users and 35% of nonusers, and slightly in 5% of users and 8% of nonusers.

Pattern of anxiolytics and/or antidepressants use
In users (**Table III**), anxiolytics were the most frequently purchased psychotropic drugs, in particular, 48% (n = 1839) of women were treated with anxiolytics, 33% (n = 1277) with anxiolytics and antidepressants and 19% (n = 732) with antidepressants alone.
The distribution of age differs among these three subgroups: while in the 34% of women who took only anxiolytics the most prevalent age was 50-64 years, in the 36% of women who took anxiolytics and antidepressants and in the 41% of women who took antidepressants alone, the most prevalent age was 35-49 years.
Among women taking only anxiolytics, benzodiazepines represented the 94% of prescribed drugs. Among the women taking only antidepressants, SSRIs represented the 59% of prescribed drugs

followed by SNRIs (17%) and tricyclic (15%). Among the women treated with both anxiolytics and antidepressants the most prescribed combination was benzodiazepines + SSRIs (51%), followed by benzodiazepines + SNRIs (17%) and benzodiazepines + tricyclic (15%).
Both antidepressants and anxiolytics were mostly took for over six months and had a positive impact on women's treatment satisfaction.

Risk factors for anxiolytics and/or antidepressants use
After the unconditional logistic regression analysis (**Table IV**), of the 15 stressful life events with positive unadjusted odds ratios (**Table II**), 10 remained associated with anxiolytics and/or antidepressants treatment. This is shown by the significant odds ratio values and the very restricted confidence intervals.
On analysing the other variables, among the users women we observed the association with the following factors (**Table V**, **Table VI**): separation/divorce, living alone, living with family or friends, unemployment, currently seen by a psychologist/psychiatrist, alimentary tract and metabolism, cardiovascular and nervous system drugs.

DISCUSSION

To our knowledge this study is the largest epidemiological survey conducted in the pharmacy setting in Italy. This is also the first Italian research about stressful life events and social health factors in women that use or not use anxiolytic and/or antidepressant drugs. To date no similar studies, both on the male population and on the general population, have been conducted in the Veneto Region and in Italy.
On the whole, the data suggest that in the population selected the perceived frequency of stressful life events was high, and that their impact on well-being was severe. These findings emerged both in women receiving an anxiolytic and/or an antidepressant drug and in women not taking these medications. This is in line with clinical and research evidence that indicates the profound, detrimental impact of stressful life events, traumas and major losses on women's physical and mental health status.[4,23,24]
An association between life events and anxiolytic and/or antidepressant use was observed. This association was particularly significant for the events occurred in the relationship sphere such as death and problems with the family and close friends and for aspects connected to work and financial difficulties.
Separation/divorce, unemployment, living alone, living with others (family or friends) were observed to be associated with an increased risk of anxiolytics and/or antidepressants use. Present findings confirm the previous studies have shown that women and those who are divorced, separated or widowed, unemployed are all more likely to seek and receive treatment for common mental disorders.[25]
In the literature no major differences are seen between the genders in exposure and sensitivity to the depressogenic effects of stressful life events.[4,5] However, men and women may differ in the types of traumatic and other stressful events they experience.[1] Women have a broadly higher risk for most or all categories of stressful life events,[26,27] while men reported more traumatic events particularly related to the job – legal – robbery - work.[1,4,5] Our data supports these observations but highlights the effect of income-related events in user and nonusers women as was observed in men. [1,4,5]
Our data may be interpreted as a medicalisation of life events that would have required social solutions: it is not so straightforward that troubles at work, financial difficulties or problems concerning personal security lead to psychotropic drug prescriptions and use.[9]
Social structural factors appear to play an important role in determining women's mental health.[28] Pressures created by women multiple roles in society as partners, caregivers and workers throughout their lifetime, associated with factors such as living alone, poverty, domestic violence and sexual abuse, combine to account for women's poor mental health.[29] Women provide the majority of informal care for spouses, parents, parents-in-law, friends and neighbours, and play many roles as caregiving, hands-on health providers, care managers, friends, companions, surrogate decision-makers and advocates.[22,30]
A large amount of research literature has consistently documented the role of severe life events as a risk factor for depression,[31] but few data exist to help explain (a) why people taking psychotropic drugs reported a substantial number of life events and (b) how this association correlates with a greater negative impact of life events on people's mental health. Downing and Rickels[32] found that the frequency of favourable and unfavourable events did not differ among psychiatric outpatients treated with chlordiazepoxide, or with diazepam, or receiving placebo. Monroe et al.[33] reported a

significant interaction between specific types of non-severe life events and medication (imipramine) in individuals with recurrent depression. Nevertheless, as this study was conducted by pharmacists in a community setting it was not possible to make a formal diagnosis of depression/anxiety and therefore we are not in a position to comment on the appropriateness of the therapy.
We can, however, reflect upon the psychotropic medication use. Only 26% of the women treated with an anxiolytic and/or an antidepressant drug was supported by a psychologist or a psychiatrist, and 3% by a social worker. As Harman reported,[34] the increasing of mental health treatment might be due to change in locus of treatment from the specialist sector to the primary care sector, the availability of SSRIs (the most prescribed drugs in our sample), and the cost containment pressures (financial difficulties were reported by the 16% of the women users). Moreover, considering the duration of anxiolytic and antidepressant treatment, we can also comment that the patterns of anxiolytic and antidepressant use were, in fact, very similar. They were characterised by long-term drug taking, over a period of at least 6 months. This use of anxiolytics (benzodiazepines) is clearly in contrast with treatment recommendations that suggest use in the short term only.[35,36] Moreover, we observed that 34% of women exposed to anxiolytics were 50 to 64 years old and 30% were 65 or older. The use of anxiolytics in older age, as it has been documented in many other studies, is associated with adverse effects including daytime sedation, ataxia, slowed psychomotor performance and risk of hip fracture.[37-40]
We found that similar dosage regimens were adopted for antidepressant and anxiolytic treatments and their concomitant use was very frequent. Spolaor[41] showed that the increase in total consumption of antidepressants in primary health care in Italy depends on the fact that these medicines are used not only in the treatment of depression but also in the treatment of panic attacks, agoraphobia, post-traumatic stress disorders and other anxiety disorders.
We additionally observed a strong association between anxiolytic and antidepressant use and exposure to cardiovascular and alimentary tract and metabolism drugs. This was in line with data on drug use in Italy in 2008. In fact, these medications were the most frequently used classes of drugs.[11] Robert[42] and Gorman[43] have described a substantial association between depression and the risk of cardiac mortality, but also between depression and cognitive impairment, increased waist-to-hip ratio, decreased bone mineral density, hypertension and type 2 diabetes.
Moving from the findings of the research, it is clear that community pharmacists as primary care health professionals are in a good position to contribute to the management of mental disorders.[11,14,44] They may play a critical role in optimizing the use of medications for mental illnesses.[11,15,45] Pharmacies are geographically well distributed and easy to access, they may offer an informal environment well placed to provide services for community-dwelling patients who have to care for themselves.[46,47] Community pharmacists are often the first clinicians citizens see when they have health problem, thus they should embrace their responsibility to increase clinical outcomes of patients.[48] This position enables them to provide several services important to mental health care, such as: providing information about pharmacotherapy, monitoring and supervising drug use, enhancing medication adherence, monitoring treatment effectiveness, identifying adverse effects, and referring to their physician if indicated.[47]

Limitation

In addition to the absence of a diagnosis of anxiety or depression, other limitations of the present study were the possibility of selection bias due to the recruitment and interviewer of women by pharmacists, and the potential bias associated with self-rated questionnaires.[49]
Lack of blinding is an inevitable defect of interview methods that yield detailed and qualitatively rich data. Pharmacist and women (both users and nonusers) expectation may have affected the results, but to what extent we do not know. This may be read in light of the Hawthorne effect,[50] a form of reactivity whereby subjects improve or modify an aspect of their behavior being experimentally measured simply in response to the fact that they are being studied. As a consequence, the frequency of life events as well as their impact on women's well-being may have been overestimated or, even, underestimated.
Another potential limit is based on the participants' self-reported levels of life stress frequency and severity. It is possible that stressful life events occurring in the environment caused cognitive and/or emotional distress that led participants to use medications, but it is also possible that individuals who are more likely to use psychiatric medications are also more likely to report having experienced more (or more severe) recent life stress. This issue could be exacerbated by the fact that the sample was drawn from persons visiting community pharmacies (i.e., sampling/selection bias).[51,52,53]
Despite these limitations, the large sample size (n = 11357) was considered a major strength of this study. This indicates that mental health issues are of interest both for women and for the participating community pharmacists.

CONCLUSIONS

The findings from this study has suggested that a large sample of Italian women, either receiving an anxiolytic and/or an antidepressant drug or not taking these medications, perceived several negative life events with a severe impact on their well-being. A significant association between stressful life events and anxiolytics and/or antidepressants use was observed. It was mainly associated with the relationship sphere and related to death, worries about family and close friends, work and financial difficulties. The patterns of anxiolytic and antidepressant treatment were very similar, characterised by long-term drug taking, over a period of at least 6 months.
Future researches are therefore needed to investigate the motivation of the use of anxiolytics/antidepressants in relation to the occurrence of life events and to the socio-demographics and socioeconomic characteristics, and the association of their use with patient's psychological or psychosocial changes. In this context, community pharmacies and pharmacists represent a potential area for promoting epidemiological research on mental health which warrants further investigation and exploitation.

Acknowledgements
We acknowledge Simonetta Tregnago President of the Equal Opportunities Commission of Veneto and all the Commission, which supported the project by a grant.
The author would like to offer deep thanks to all the community pharmacists of Veneto, who played a significant role in this research.
We would like to thank Prof. Roberto Leone (Clinical Pharmacology Unit University of Verona) for their support and encouragement; Dott. Ugo Moretti (Clinical Pharmacology Unit University of Verona), Dott.ssa Laure Pourcel (Service de Pharmacologie Clinique Faculté de Médecine, CEIP de Toulouse) and Dott.ssa Laura Bisoffi (Head of Biostatistics and Research Support Unit University of Verona) for their help with the statistics; Anna Carreri (University of Verona) for his help in the research activities.

Funding
This project was supported by Equal Opportunities Commission of Veneto Region

Conflict of interest
The authors have no financial or personal conflict of interest in this study.

REFERENCES

1. Hatch SL, Dohrenwend BP. Distribution of traumatic and other stressful life events by race/ethnicity, gender, SES and age: a review of the research. Am J Community Psychol. 2007;40:313-332.
2. Duetz MS, Abel T, Niemann S. Health measures: differentiating associations with gender and socio-economic status. Eur J Public Health. 2003;13:313-319.
3. World Health Organization. Improving Access and Use of Psychotropic Medicines. Full Report 2004. http://www.who.int/mental_health/policy/essentialpackage1/en/index1.html. Accessed March 15, 2010.
4. Kendler KS, Thornton LM, Prescott CA. Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. *Am J Psychiatry*. 2001;158:587-593.
5. Keita GP. Psychosocial and cultural contributions to depression in women: considerations for women midlife and beyond. *J Manag Care Pharm*. 2007;13:S12-S5.
6. Kessler RC, Price RH, Wortman CB. Social factors in psychopathology: stress, social support, and coping processes. *Annu Rev Psychol*.1985;36:531-572.
7. Schnurr PP, Green BL. Understanding relationships among trauma, post-traumatic stress disorder, and health outcomes. *Adv Mind Body Med*. 2004;20:18-29.
8. Manninen BA. Medicating the mind: a Kantian analysis of overprescribing psychoactive drugs. *J Med Ethics*. 2006;32:100-105.
9. Eurispes - Istituto di studi politici, economici e sociali, editor. XXII° Rapporto Italia 2010. Full Report 2010.

http://www.eurispesitalia.it/index.php?option=com_content&view=article&id=1095:rapporto-italia-2010&catid=47:rapporto-italia&Itemid=222
Accessed March 15, 2010.
10. Agenzia Italiana del Farmaco. L'uso dei Farmaci in Italia. Rapporto nazionale anno 2008. Full Report 2009. http://www.agenziafarmaco.it/allegati/rapporto_osmed_2008.pdf Accessed March 15, 2010.
11. Bell S, McLachlan AJ, Aslani P, Whitehead P et al. Community pharmacy services to optimize the use of medications for mental illness: a systematic review. *Aust New Zealand Health Policy.* 2005;2:29-39.
12. Bell JS, Rosen A, Aslani P, Whitehead P, Chen TF. Developing the role of pharmacists as members of community mental health teams: perspectives of pharmacists and mental health professionals. Res Social Adm Pharm. 2007;3:392-409.
13. Black E, Murphy AL, Gardner DM. Community pharmacist services for people with mental illnesses: preferences, satisfaction, and stigma. *Psychiatr Serv*. 2009;60:1123-1127.
14. Bell JS, Whitehead P, Aslani P, Sacker S et al. Design and implementation of an educational partnership between community pharmacists and consumer educators in mental health care. *Am J Pharm Educ*. 2006;70:1-6.
15. Finley PR, Crismon ML, Rush AJ. Evaluating the impact of pharmacists in mental health: a systematic review. *Pharmacotherapy*. 2003;23:1634-1644.

16. Data from the Professional Associations and Association of Owners of Italian Pharmacies - Federfarma - 2008.
17. D'Incau P, Gangemi M, Tubini J et al. La formazione come ricerca nella pratica quotidiana del farmacista. *Diaologo sui Farmaci*. 2009;3:116-117.
18. Howland RH. Somatic therapies for seasonal affective disorder. *J Psychosoc Nurs*. *Ment Health Serv*. 2009;47:17-20.
19. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2010. Full Report 2009.
www.whocc.no/filearchive/publications/2010guidelines.pdf. Accessed March 15, 2010.
20. Brugha TS, Cragg D. The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta Psychiatrica Scand*. 1990;82:77-81.
21. Prince MJ, Harwood RH, Blizard RA, et al. Social support deficits, loneliness and life events as risk factors for depression in old age. The Gospel Oak Project VI. *Psychol Med*. 1997;27:323-32.
22. Paykel ES. The interview for recent life events. *Psychol Med*. 1997;27:301-310.
23. Leserman J, Zhiming L, Yuming JBH et al. How multiple types of stressors impact on health. *Psychosom Med*. 1998;60:175-181.
24. Ormel J, Oldehinkel AJ, Brilman EI. The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *Am J Psychiatry*. 2001;158:885-891.
25. Colman I, Croudace TJ, Wadsworth ME, Jones PB. Factors associated with antidepressant, anxiolytic and hypnotic use over 17 years in a national cohort. *J Affect Disord*. 2008;110:234-240.
26. Brown GW, Birley JLT: Crises and life changes and the onset of schizophrenia. *J Health Soc Behav.*1968; 9:203–214.
27. Bebbington PE, Tennant C, Hurry J: Adversity in groups with an increased risk of minor affective disorder. *Br J Psychiatry*. 1991; 158:33–48.
28. Dentona M, Walters V. Gender differences in structural and behavioural determinants of health: an analysis of the social production of health. *Soc Sci Med*. 1990;48:1221-1235.
29. The Women's Health Council. Improving the mental health of the population. Towards a strategy on mental health for the European Union. Full Report 2006.
http://www.whc.ie/publications/26. Accessed March 15, 2010.
30. Navaie-Waliser M, Feldman PH, Gould DA, Levine C, Kuerbis AN, Donelan K. When the caregiver needs care: the plight of vulnerable caregivers. *Am J Public Health*. 2002;92:409-413.
31. Brown GW, Harris TO. Depression. In G. W. Brown and T. O. Harris (Eds.). *Life Events and Illness*. London: Guilford Press;1989. pp.49-93.
32. Downing RW, Rickels K. The impact of favorable and unfavorable life events on psychotropic drug response. *Psychopharmacology*. 1982;78:97-100.
33. Monroe SM, Torres LD, Guillaumot J et al. Life stress and the long-term treatment course of recurrent depression: III. Nonsevere life events predict recurrence for medicated patients over 3 years. *J Consult Clin Psychol*. 2006;74:112-20.
34. Harman JS, Rollman BL, Hanusa BH, Lenze EJ, Shear MK. Physician office visits of adults for anxiety disorders in the United States, 1985-1998. *J Gen Intern Med*. 2002;17:165-172.

35. National Institute for Health and Clinical Excellence, editor. Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. Full Report 2004. http://guidance.nice.org.uk/CG22. Accessed March 15, 2010.
36. National Institute for Health and Clinical Excellence, editor. Depression: management of depression in primary and secondary care - NICE guidance. Full Report 2004. http://guidance.nice.org.uk/CG23. Accessed March 15, 2010.
37. Fourrier A, Letenneur L, Dartigues JF, Moore N, Bégaud B. Benzodiazepine use in an elderly community-dwelling population. Characteristics of users and factors associated with subsequent use. *Eur J Clin Pharmacol*. 2001;57:419–425.
38. Lechevallier N, Fourrier A, Berr C. Benzodiazepine use in the elderly: the EVA Study. *Rev Epidemiol Sante Publique*. 2003;51:317–326.
39. Gleason PP, Schulz R, Smith NL, Newsom JT, Kroboth PD, Kroboth FJ, Psaty BM. Correlates and prevalence of benzodiazepine use in community-dwelling elderly. *J Gen Intern Med.* 1998;13:243–250.
40. Johnell K, Fastbom J, Rosén M et al. Inappropriate drug use in the elderly: a nationwide register-based study. *Ann Pharmacother*. 2007;41:1243–1248.
41. Spolaor A, Font M, Castellani L. et al. Il dibattito sugli antidepressivi. *Diaologo sui Farmaci.* 2000;1:25-32.
42. Robert HF, Wittchen HU, Pfister H, Lieb R. Life events and changes in the course of depression in young adults. *Eur Psychiatry*. 2002;17:241-53.
43. Gorman JM. Gender differences in depression and response to psychotropic medication. *Gend Med*. 2006;3:93-109.
44. Scheerder G, De Coster I, Van Audenhove C. Pharmacists' role in depression care: a survey of attitudes, current practices, and barriers. *Psychiatr Serv*. 2008;59:1155-1160.
45. Hare SK, Kraenow K. Depression screenings: developing a model for use in a. J *Am Pharm Assoc*. 2008;48:46-51.
46. Lambert B L. Face and politeness in pharmacist-physician interaction. *Soc Sci Med*. 1996;43:1189-1198.
47. Scheerder G, De Coster I, Van Audenhove C. Community pharmacists' attitude toward depression: a pilot study. *Res Social Adm Pharm*. 2009;5:242-252.
48. Desai HD, Jann MW. Major depression in women: a review of the literature. *J Am Pharm Assoc (Wash)*. 2000;40:525-537.
49. Rothman KJ, Greenland S. *Case-Control Studies. In: Modern Epidemiology*, 2nd edition, eds. K. J. Rothman and S. Greenland. Philadelphia, PA: Lippincott-Raven; 1998.
50. McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, et al. The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol*. 2007;7:30.
51. Monroe SM. Major and minor life events as predictors of psychological distress: further issues and findings. J Behav Med. 1983;6:189-205.
52. Cochran SD, Hammen CL. Perceptions of stressful life events and depression: a test of attributional models. J Pers Soc Psychol. 1985;48:1562-1571.
53. Dohrenwend BP. Inventorying stressful life events as risk factors for psychopathology: Toward resolution of the problem of intracategory variability. Psychol Bull. 2006 May;132:477-495.

TABLES

Table I. Demographics characteristics of women sample (*N* = 11357) and unadjusted odds ratios.

	Users (3848)		Nonusers (7509)		OR (95% CI)
	n	%	*n*	%	
Age					
<35	410	11	974	13	0.80 (0.71-0.91)
35-49	1249	32	2538	34	0.94 (0.87-1.02)
50-64	1273	33	2490	33	1.00 (0.92-1.08)
≥ 65	916	24	1507	20	1.24 (1.13-1.37)
Provenance area*					
No data	143	4	270	4	
Urban	2476	64	4838	64	1.00 (0.92-1.08)
Rural	1229	32	2401	32	1.00 (0.92-1.08)

*A rural area is defined as an area with a population not exceeding 5.000 inhabitants; an urban area is defined as an area with a population greater than 5.000 inhabitants.

Table II. Percentage* of type of stressful life events description (*N* = 11357) and unadjusted odds ratios.

Life events	Users (3848)		Nonusers (7509)		OR (95% CI)
	n	%	n	%	
Being a victim of a violent act out of family	82	2	68	1	2.38 (1.70-3.34)
Being a victim of a violent act in family	161	4	139	2	2.32 (1.83-2.93)
Close relative was a victim of a violent act out of family	49	1	97	1	0.99 (0.69-1.41)
Close relative was a victim of a violent act in family	68	2	95	1	1.40 (1.01-1.94)
Close relative death	1395	36	2211	29	1.36 (1.25-1.48)
Other relative death	778	20	1545	21	0.98 (0.89-1.08)
Major personal illness or injury	919	24	1102	15	1.82 (1.65-2.01)
Major close relative illness or injury	965	25	1628	22	1.21 (1.10-1.33)
Miscarriage or abortion	278	7	494	7	1.11 (0.95-1.29)
Serious problems with a dear friend, a neighbour or a relative	522	14	855	11	1.22 (1.09-1.37)
Broken relationship	544	14	684	9	1.64 (1.45-1.86)
Separation or divorce	365	9	396	5	1.88 (1.62-2.14)
Unemployment	193	5	277	4	1.38 (1.14-1.67)
Employment	149	4	223	3	1.32 (1.06-1.63)
Toubles at work	353	9	478	6	1.49 (1.28-1.72)
Financial difficulties	612	16	866	12	1.45 (1.30-1.62)
Lost something important	283	7	606	8	0.90 (0.78-1.05)
Other	408	11	421	6	2.00 (1.73-2.31)

* Total category events greater than the total number of cases and controls as multiple responses permitted

Table III. Percentage of age, class of drugs, duration and satisfaction of treatment of users (*N* = 3848*)*.

	Anxiolytics (1839)		Antidepressants (732)		Antidepressants+ anxiolytics (1277)	
	n	%	*n*	%	*n*	%
Age						
<35	163	9	119	16	128	10
35-49	489	27	299	41	461	36
50-64	629	34	219	30	425	33
≥ 65	558	30	95	13	263	21
Type of molecules*						
No data	37	2	18	2	18	2
BDZ	1727	94	—	—	—	—
Other anxiolytics	63	3	—	—	—	—
BDZ + other anxiolytics	12	1	—	—	—	—
SSRIs	—	—	434	59	—	—
Tricyclic	—	—	112	15	—	—
SNRIs	—	—	126	17	—	—
MAOIs	—	—	42	6	—	—
BDZ + Tricyclic	—	—	—	—	186	15
BDZ + SSRIs	—	—	—	—	651	51
BDZ + SNRIs	—	—	—	—	222	17
Different combinations	—	—	—	—	200	15
Duration						
Null	109	6	36	5	20	2
First usage	67	4	39	5	24	2
For 1-6 months	208	11	152	21	105	8
Over 6 months	1455	79	505	69	835	65
Satisfaction						
Yes	1490	81	574	78	1061	83
No	349	19	158	22	216	17

* BDZ= benzodiazepines; Other anxiolytics = zopiclone, zolpidem; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; MAOIs = monoamine oxidase inhibitors (Italian drug classification)[5].

Table IV. Risk of use anxiolytics and/or antidepressants and the occurrence of stressful life events determined by unconditional logistic regression

	Total (11357)		Users (3848)		Nonusers (7509)		OR_{adj} (95% CI)	P-Value*
Variable	**n**	**%**	**n**	**%**	**n**	**%**		
Being a victim of a violent act outside the family								
No	11207	99	3766	98	7441	99	1.00	
Yes	150	1	82	2	68	1	1.27 (1.01-1.60)	0.0352
Being a victim of a violent act in the family								
No	11057	97	3687	96	7370	98	1.00	
Yes	300	3	161	4	139	2	2.31 (1.83-2.91)	< 0.0001
Death of a close relative								
No	7751	68	2453	64	5298	71	1.00	
Yes	3606	32	1395	36	2211	29	1.246 (1.17-1.32)	0.0003
Major personal illness or injury								
No	9336	82	2929	76	6407	85	1.00	
Yes	2021	18	919	24	1102	15	1.544 (1.44-1.65)	< 0.0001
Major close relative illness or injury								
No	8764	77	2883	75	5881	78	1.00	
Yes	2593	23	965	25	1628	22	1.15 (1.08-1.22)	< 0.0001
Broken relationship								
No	10089	89	3304	86	6825	91	1.00	
Yes	1268	11	544	14	684	9	1.37(1.25-1.49)	< 0.0001
Separation or divorce								
No	10596	93	3483	91	7113	95	1.00	
Yes	761	7	365	9	396	5	1.46 (1.28-1.67)	< 0.0001
Trouble at work								
No	10526	93	3495	91	7031	94	1.00	
Yes	831	7	353	9	478	6	1.44 (1.30-1.59)	< 0.0001
Financial difficulties								
No	9879	87	3236	84	6643	88	1.00	
Yes	1478	13	612	16	866	12	1.09 (1.01-1.18)	0.0198
Other								
No	10528	93	3440	89	7088	94	1.00	
Yes	829	7	408	11	421	6	2.07 (1.88-2.27)	< 0.0001

* Adjusted p<0.05 (after logistic regression)

Table V. Risk of use anxiolytics and/or antidepressants and social-demographics and health factors determined by unconditional logistic regression.

	Total (11357)		Users (3848)		Nonusers (7509)		OR_{adj} (95% CI)	P-Value*
Variable	**n**	**%**	**n**	**%**	**n**	**%**		
Marital status								
Married	6832	60%	2085	54	4747	63	1.00	
Single	1756	15%	590	15	1166	16	0.81 (0.70-0.94)	0.0086
Separeted/Divorced	431	4%	507	13	665	9	1.21 (1.03-1.42)	0.0166
Cohabitation status								
With spouse (or cohabitant)	3291	29%	1087	28	2204	29	1.00	
With spouse (or partner) and children	3739	33%	1046	27	2693	36	0.81 (0.75-0.87)	< 0.0001
Alone	1906	17%	781	20	1125	15	1.18 (1.01-1.37)	0.0270
With others (family or friends)	1231	11%	458	12	773	10	1.29 (1.10-1.52)	0.0014
Employment status								
Housewife	5061	45%	1829	48	3232	43	1.00	
Unemployed	444	4%	222	6	222	3	1.54 (1.34-1.77)	< 0.0001
Employed	4268	38%	1648	43	3741	50	0.76 (0.70-0.82)	< 0.0001
Ability to perform normal daily activities								
No	289	3%	142	4	147	2	1.00	
Yes	10966	97%	3681	96	7285	97	0.80 (0.75-0.86)	< 0.0001
Currently seen by a psychologist / psychiatrist								
No	9982	88%	2801	73	7181	96	1.00	
Yes	1216	11%	1015	26	201	3	2.66 (2.45-2.89)	< 0.0001
Currently seen by a social worker								
No	10990	97%	3688	96	7302	97	1.00	
Yes	183	2%	117	3	66	1	0.44 (0.40-0.48)	< 0.0001

* Adjusted p<0.05 (after logistic regression)

Table VI. Risk of use anxiolytics and/or antidepressants and other drugs** and therapeutic remedies determined by unconditional logistic regression

	Total (11357)		Users (3848)		Nonusers (7509)		OR_{adj} (95% CI)	P-Value*
Variable	**n**	**%**	**n**	**%**	**n**	**%**		
(A) Alimentary tract and metabolism drugs								
No	9491	84	3124	81	6367	85	1.00	-
Yes	1866	16	724	19	1142	15	1.09 (1.02-1.17)	1.0242
(C) Cardiovascular system drugs								
No	8172	72	2628	68	5544	74	1.00	-
Yes	3185	28	1220	47	1965	39	1.11 (1.04-1.18)	1.0418
(D) Dermatologicals drugs								
No	10750	95	3682	96	7068	94	1.00	-
Yes	607	5	166	6	441	9	0.67 (0.60-0.76)	0.6005
(G) Genito urinary system and sex hormones drugs								
No	10377	91	3570	93	6807	91	1.00	-
Yes	980	9	278	11	702	14	0.77 (0.70-0.85)	0.7057
(H) Systemic hormonal preparations drugs								
No	10650	94	3634	94	7016	93	1.00	-
Yes	707	6	214	8	493	10	0.80 (0.71-0.89)	0.7192
(J) Anti-infectives for systemic use drugs								
No	11029	97	3781	98	7248	97	1.00	-
Yes	328	3	67	3	261	5	0.49 (0.41-0.58)	0.4172
(N) Nervous system drugs								
No	11050	97	3659	95	7391	98	1.00	-
Yes	307	3	189	7	118	2	2.00 (1.71-2.35)	1.7135
(R) Respiratory system drugs								
No	10661	94	3680	96	6981	93	1.00	-
Yes	696	6	168	6	528	11	0.55 (0.49-0.62)	0.4936
Herbal remedies and/or homeopathic products use								
No	7920	70	2896	75	5024	67	1.00	-
Yes	3437	30	952		2485		0.69 (0.65-0.73)	0.6514

* Adjusted p<0.05 (after logistic regression)
** Classification according to the first level of the Anatomical Therapeutic Chemical -ATC- classification system.[16]

ANNEX 3.

Paola D'Incau, M Lapeyre-Mestre, M Sa´inz, M Donati, A Carvajal. **Gender differences of ADRs related to psychotropic drug use: a survey from France, Italy and Spain**. Basic & Clinical Pharmacology & Toxicology. 2010; 107 (Suppl. 1): 162–692.

It is well recognized that being female appears to be a risk factor for developing ADRs. A number of studies clearly suggest that ADRs are50 to 75% more likely in women than men. At the same time, nervous system agents represents one of the most frequent drug classes reported(20%) to elicit adverse events. A female propensity to experience or report drug-related adverse effects may result from gender-related differences in drug exposure as well as in the number of drugs prescribed, in the drug pharmacokinetics and pharmacodynamics. Nonetheless, the reasons for this increased risk in female patients are not entirely clear, notably whether adverse drug reactions among women reflect an inappropriate use of psychotropic medicines.

The results from the European Study of the Epidemiology of Mental Disorders (ESEMED) andfrom the Ordonnances Suspectes Indicateur d'Abus Possible (OSIAP)project suggest that among European countries, France, Italy and Spain reordered one of the highest percentages of psychotropic drug use.

On the basis of these assumptions, the aim of this study is to compare in males and females incidence, type, seriousness and drugs involved in ADRs reported in a regional pharmacovigilance centre of each of these countries respectively, Midi-Pyre´ne´es, Veneto and Castilla-Leon, using spontaneously reported cases between 2007 and 2009. This analysis will also compare the incidence, type, seriousness and psychotropic drugs involved in ADRs in males and females, as spontaneously reported to these three regional pharmacovigilance centres.

Van der Heyden JHA et al. Pharmacoepidemiology and Drug Safety2009;18: 1101–1110

Paola D'Incau, M Lapeyre-Mestre, M Sa´inz, M Donati, A Carvajal, A. Conforti. **Gender differences of ADRs related to psychotropic drug use: a survey from France, Italy and Spain.** II°National Congress on Gender Medicine, 21-23th October, 2010, Padua, Italy. http://www.gendermedicine.org.

Background: It is well recognized that being female appears to be a risk factor for developing ADRs. Nonetheless, the reasons for this increased risk in female patients are not entirely clear, notably whether adverse drug reactions among women reflect an inappropriate use of psychotropic medications.

Objectives: The aim of this study is to analyze the difference between women and men of adverse drug reactions of psychotropic using spontaneously reactions reported in a regional pharmacovigilance centre of Midi-Pyrénées (France), Veneto (Italy) and Castilla-Leon (Spain).

Methods: Within the French, Italian and Spanish Pharmacovigilance System databases, the case/non-case method was used to measure the association with the exposure of psychotropic medications of interest and gender.

Results: A total of 967 patients were included in the study, 592 (61%) were female and 375 (39%) were male ($p< 0.001$). Mean age of the study population was 51 years (range 08-97). The association between the exposure of psychotropic medications of interest and gender was statistically significant for women, especially who taken antidepressants.

Conclusions: The present study indicates that female sex is a risk factor for the development of ADRs related to psychotropic drugs especially to antidepressants.

Key words: adverse drug reactions, psychotropic drugs, gender