Pharmacoepidemiology of psychoactive medication in adult patients in the psychiatric department of Durango General Hospital

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Psychiatric diseases have become a public health problem owing to their increased prevalence. An option for their treatment is psychoactive medications, which are associated with multiple adverse effects. The purpose of this study was to determine the pharmacoepidemiology of psychoactive medication and the prevalence of psychiatric disease in adult patients seen at the Psychiatry Department at Durango General Hospital. Clinical histories of the patients were reviewed for patients over 18 years of age that were seen at the outpatient clinic of the Psychiatry Department at Durango General Hospital that were diagnosed at this hospital with psychiatric conditions requiring psychoactive medication for their treatment. The study was conducted between January 2009 and February 2010. The most commonly diagnosed conditions were the neurotic disorders, stress related disorders, and somatization disorders (42.9%), with the most common sub-classification being major depression with anxiety (26.3%). Seventy six percent of patients received more than one medication for their treatment. The most commonly prescribed medications were the selective serotonin reuptake inhibitors, with fluoxetine being the most prescribed medication (42.2%). Anxiolytics were the second most prescribed group, with clonazepam being the most prescribed medication within this group (67.8% of patients). Contrasting with the clinical practice guidelines, in which single drug therapy is recommended for most of the psychiatric diseases, only 23.24% of the patients received single drug therapy. The age group with most prescriptions was between 30 and 59 years of age.

Keywords: psychoactive medication, psychiatric disease, pharmacoepidemiology, adults

INTRODUCTION

Psychiatric disorders have become a high priority public health problem, especially in Latin America, where their prevalence has increased. (Kohn et al., 2005) Mexico's statistics follow the same trend, showing that 4 out the 10 most handicapping diseases are classified within the neuropsychiatric cluster (schizophrenia, depression, obsessive-compulsive disorder, and alcoholism) and this numbers are expected to increase. (Medina-Mora et al., 2003)

Another worrying statistic regarding mental health in Mexico was reported in the First National Survey of Psychiatric Disorders were a lifelong prevalence of psychiatric disorders was estimated to be 26.1%, a number that is still below what is reported for countries like the United States of America and the Netherlands but it is higher than some countries, like Turkey (Medina-Mora et al., 2007) Also, the World Bank statistics estimate a 22% increase in the age group between 15 and 49 years of age in Latin America from

the year 2000 to 2015. With this age group having the highest risk for psychiatric disorders there will be an increase in the need for psychiatric attention in our country. (Kohn et al., 2005)

To face this increase in psychiatric disorders there is a need to understand their prevalence, treatment deficiencies, and the new therapeutic options under a new approach that take into account pharmacokinetics as well as pharmacogenetics.

One of the treatment options for these diseases that have showed a great advance is psychoactive medications (antidepressives, anxiolytics, mood stabilizers, anticholinergics, and psychostimulants) (Beck et al., 2005) (Heinze et al., 2005) however, with this new therapeutic approach, more and more patients are exposed to medication that is not exempt of adverse effects. (Degner et al., 2004) (Secades-Villa et al., 2003) (Wren et al., 2003)

The use of psychoactive medication in clinical practice is linked with known variables, such as individual response to treatment and adverse effect incidence. Part of the explanation for this variability may lie within the P450 system. (Vandel et al., 2007) An example of the enzymatic group involved in the metabolism of psychoactive medication is the CYP2D6 enzyme that could be subject to genetic polymorphisms and resulting in inter-individual variability in bioavailability of drugs and pharmacokinetic processes. (Vandel el al., 2007)

In Mexico, neuropsychiatric disorders are the fifth place in morbidity statistics disease. (Frenk et al., 1999) Therefore, we are interested in knowing the prevalence of these disorders in the Durango General Hospital, as well as the prescribing patterns of the most commonly used medications for their treatment.

With these previous data and the lack of information of the adherence to guidelines and medication prescription (Verdoux et al., 2004) there is an obvious need to create pharmacoepidemiology studies that review the use and impact of psychoactive medication on our population, followed by pharmacokinetic and pharmacogenetic studies to improve the treatment schemes and offer patients a safe management of their disease.

METHODS

This study is retrospective and descriptive, taking part from January 1, 2009 to February 28, 2010.

Clinical histories of the patients were reviewed for patients over 18 years of age that were seen at the outpatient clinic of the Psychiatry Department at Durango General Hospital that were diagnosed at this hospital with psychiatric conditions requiring psychoactive medication for their treatment. The diagnoses were made by attending Psychiatrists in staff at the Durango General Hospital. The complete files were reviewed and a medication history table was designed to review all the medication received by each patient. Missing or incomplete files were not used for the analysis. Tables were designed to standardize the data gathering procedures.

The statistical analysis was done using the SPSS 17.0 software for Windows. Once the data distribution and type of scales of the variables were known we proceeded to do a comparative analysis using chi square and Kruskal-Wallis tests; accepted level of significance was $p \leq 0.05$

RESULTS

A total of 228 patients were included, 171 (75.5%) being female and 57 (25%) being male, with an average age of 40.7 ± 14.97 years of age for the female group and 43.3 ± 16.10 years of age for the male group.

Patients were classified according to the World Health Organization's International Classification of Disease (ICD-10) (The ICD-10., 1993), with the results seen in table 1. Neurotic disorders, stress related disorders and somatization disorders (ICD-10:F4) were the most prevalent (42.9%), followed by affective (mood) disorders (ICD-10:F3) (39.5%), patients with organic disorders (ICD-10:F0) (5.2%), and schizophrenia, schizotypal and delusional disorders (ICD-10:F2) (4.8%). Most patients were classified into sections F3 and F4, adding up to 82.46% of patients.

The most common psychiatric conditions found in our patients can be seen in table 2. The most common disease was mixed anxiety and depressive disorder (26.3%), followed by anxiety and dysthymic disorders (9.6% each), and then moderate depressive episode (8.8%). 8.3% of patients had recurrent depressive disorder and 6.6% had severe depressive episode, while 24.6% of patients had other disorders (bipolar disorder, organic hallucinations, mild depressive episode).

These disorders had a higher prevalence in female patients (Figure 1), especially mixed anxiety and depressive disorder, with 45 patients being female and 15 being male, as well as dysthymic disorder, with 21 female patients and 1 male patient. The difference was calculated as statistically significant ($p < 0.0047$).

Dividing our group of patients by age groups, we have the following results (Figure 2): the group with the highest number of patients with psychiatric disorders was the age group between 30-59 years of age (60% of patients), followed by the group between 18-29 years of age (23.6%), then by the patients aged 60-84 (15.7%), with the group over 85 having the lowest amount of patients (0.44%), with a statistically significant difference of $p < .0001$ between age groups.

Figure 3 shows the psychoactive medication prescribed to our patients: antidepressives were prescribed to 93.4% of patients, anxiolytics to 64%, and mood stabilizers to 47.8%.

Tables 3 through 7 shows the most prescribed

Table 1. Frequency and percentage of patients by ICD-10 general diagnostic categories at the psychiatry department of Durango General Hospital.

ICD-10 diagnostic categories	Frequency	Percentage
F0	12	5.2
F1	4	1.7
F2	11	4.8
F3	90	39.5
F4	98	42.9
F5	4	1.7
F6	6	2.6
F7	3	1.3
F9	0	0
Total	228	100

F0, Organic, including symptomatic, mental disorders
F1, Mental and behavioral disorders due to psychoactive substance use
F2, Schizophrenia, schizotypal and delusional disorders
F3, Mood [affective] disorders
F4, Neurotic, stress-related and somatoform disorders
F5, Behavioral syndromes associated with physiological disturbances and physical factors
F6, Disorders of adult personality and behavior
F7, Mental retardation
F9, Behavioral and emotional disorders with onset usually occurring in childhood and adolescence

Table 2. Disorders (diagnostic subcategories) presented in patients from the Psychiatry Department of Durango General Hospital.

Diagnosis	Percentage
Mixed anxiety and depressive disorder	26.3
Generalized anxiety disorder	9.6
Dysthymia	9.6
Moderate depressive episode	8.8
Recurrent depressive disorder	8.3
Severe depressive episode	6.6
Acute and transient psychotic disorders	3.5
Somatoform disorders	2.6
Others	24.6
Total	100

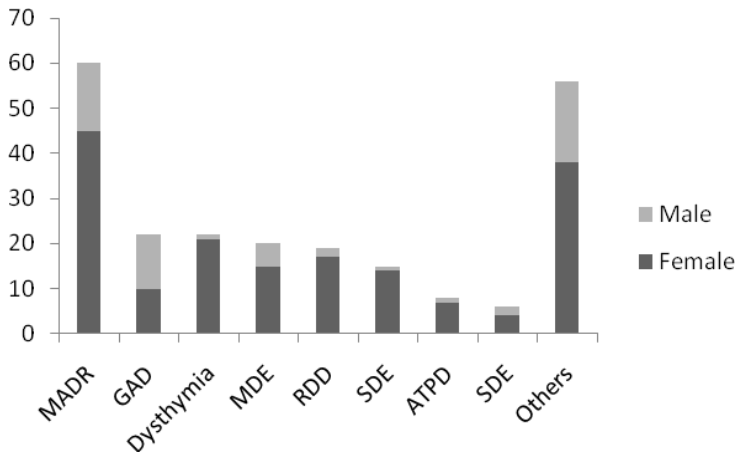

Figure 1. Pathologies according to sex in a group of 228 patients from the Psychiatry Department of Durango General Hospital
* Statistically significant differences
$\chi^2 = 22.37$*; $p < 0.0047$; Degrees of freedom = 8
MADR: Mixed anxiety and depressive disorder
GAD: Generalized anxiety disorder
MDE: Moderate depressive episode
RDD: Recurrent depressive disorder
SDE: Severe depressive episode
ATPD: Acute and transient psychotic disorders
SDE: Somatoform disorders

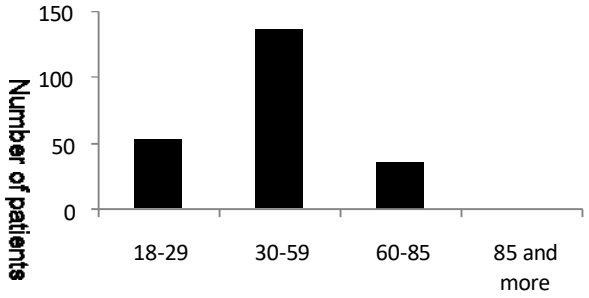

Figure 2. Frequency of psychiatric disorders according to age groups in 228 patients from the Psychiatry Department of Durango General Hospital.
Kruskal-Wallis test
$P < 0.001$*
* Statistically significant differences

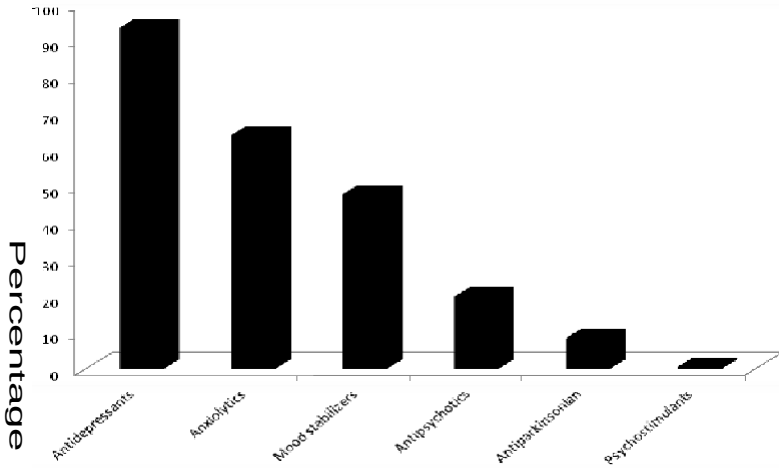

Figure 3. Distribution of psychoactive drugs used at the Psychiatry Department of Durango General Hospital.

Table 3. Antidepressants prescribed at the Psychiatry Department of Durango General Hospital.

Antidepressants		Number of patients	Percentage
SSRI			
	Fluoxetine	90	42.2
	Sertraline	79	37.0
	Paroxetine	14	6.5
	Escitalopram	4	1.9
	Citalopram	3	1.4
SSNRI			
	Venlafaxine	2	0.9
	Desvenlafaxine	1	0.4
	Milnacipran	1	0.4
TCA			
	Amitriptyline	5	2.3
	Imipramine	1	0.4
2 antidepressant therapy			
	Fluoxetine, Amitriptyline	5	2.3
	Sertraline, Amitriptylina	2	0.9
	Fluoxetine, Paroxetine	1	0.4
	Paroxetine, Trazodone	1	0.4
	Duloxetine, Venlafaxine	1	0.4
Others			
	Mirtazapine	2	0.9
	Bupropion	1	0.4
Total		213	100

medication grouped into drug families. The most prescribed antidepressants (table 3) were selective serotonin reuptake inhibitors (SSRI's) like Fluoxetine (42.2%) and Sertraline (32%). Within the anxiolytics group (table 4) benzodiazepines were used the most, especially Clonazepam (67.8%) and Alprazolam (10.9%). Regarding mood stabilizers (table 5), Valproic Acid (51.4%) and Carbamazepine (42.2%) were prescribed most frequently. In the antipsychotic drug group (table 6) atypical antipsychotics were used the most: Risperidone (68.8%) and Olanzapine (6.7%) being the two most common. The only psychostimulant

Table 4. Anxiolytics prescribed at the Psychiatry Department of Durango General Hospital.

Anxiolytics		Number of patients	Percentage
Benzodiazepines			
	Clonazepam	99	67.8
	Alprazolam	16	10.9
	Lorazepam	7	4.8
	Ethyl loflazepate	7	4.8
	Bromazepam	3	2.0
	Triazolam	2	1.4
	Diazepam	2	1.4
B-blockers			
	Metoprolol	1	0.7
	Propranolol	1	0.7
2 anxiolytic therapy			
	Clonazepam, Propranolol	4	2.7
	Alprazolam, Propranolol	3	2.0
	Bromazepam, lorazepam	1	0.7
Total		146	100

B-blocker, Beta receptor blockers.

Table 5. Mood stabilizers prescribed at the Psychiatry Department of Durango General Hospital.

Mood stabilizers	Number of patients	Percentage
Valproate	56	51.4
Carbamazepine	46	42.2
phenytoin	1	0.9
Lamotrigine	1	0.9
Gabapentin	1	0.9
Pregabalin	1	0.9
2 mood stabilizers therapy		
Valproate, phenytoin	2	1.8
Valproate, Carbamazepine	1	0.9
Total	109	100

Table 6. Antipsychotics prescribed at the Psychiatry Department of Durango General Hospital.

Antipsychotics		Number of patients	Percentage
Atypical			
	Risperidone	31	68.8
	Olanzapine	3	6.7
Typical			
	Trifluoperazine	3	6.7
	Haloperidol	1	2.2
	Levomepromazine	1	2.2
Others			
	Lithium	1	2.2
2 or 3 antypsychotic therapy			
	Risperidone,Levomepromazine	1	2.2
	Risperidone, Lithium	1	2.2
	Risperidone, Haloperidol	1	2.2
	Risperidone, Trifluoperazine	1	2.2
	Risperidone, Levomepromazine, Haloperidol	1	2.2
Total		45	100

Table 7. Psychostimulants, antiparkinsonian prescribed at the Psychiatry Department of Durango General Hospital.

Psichostimulants, antiparkinsonian		Number of patients	Percentage
Psychostimulants	Modafinil	1	100
Total		1	100
Antiparkinsonian			
	Biperidene	18	94.7
	Trihexyphenidyl	1	5.3
Total		19	100

that was used was Modafinil (table 7). Biperidene (94.7%) was the anticholinergic drug that was used the most (table 7). The combined medication that was used the most was the combination of Amitriptyline, Perphenazine, and Diazepam (Adepsique®). Within non-psychoactive medication prescribed in the psychiatry clinic the most common drugs were Omeprazole (36%) and Cinnarizine (32%).

Table 8 shows the distribution of patients by number of prescribed drugs. 23.2% of patients received monotherapy, being the most common mode of therapy, followed by therapy with four medications (22.4% of patients). 21.92% of patients received two medications, while 20.61% received three, 7.9% received five, 3.1% received 6 different drugs, and 0.9% received 7.

Patients were also divided by number of medications received and gender. Monotherapy was more common in female patients than male patients, with 25.73% and 15.8% of patients, respectively. Therapy with two drugs was prescribed for 21.05% of female patients and 24.6% of male patients; three drugs were prescribed to 20.46% of females and 21% of males; and four drug therapy was given to 22.22% of females and 22.8% of males.

Table 9 shows the most commonly used medication combinations in these patients. The most commonly used combination was Sertraline, Clonazepam, and Valproate (6.1%) followed by Fluoxetine, Clonazepam, Carbamazepine and Adepsique® (Amitriptyline, Perphenazine, and Diazepam) with a 5.3% of patients.

Table 8. Frequency and percentage of patients requiring various pharmaceuticals according to gender at Durango General Hospital.

Number of prescribed medications	Female Frequency	Percentage	Male Frequency	Percentage	Total number of patients	Total Percentage
1	44	25.73	9	15.8	53	23.2
2	36	21.05	14	24.6	50	21.9
3	35	20.46	12	21	47	20.6
4	38	22.22	13	22.8	51	22.4
5	11	6.43	7	12.3	18	7.9
6	6	3.5	1	1.7	7	3.1
7	1	0.58	1	1.7	2	0.9
Total	171	100	57	100	228	100

Table 9. Combinations of psychoactive medication at the Psychiatry Department of Durango General Hospital.

Combinations of psychotropics	Number of patients	Percentage
Sertraline + Clonazepam + Valproate	14	6.1
Fluoxetine+ Clonazepam + Carbamazepinae+ Adepsique®	12	5.3
Fluoxetine + Clonazepam + Valproate	12	5.3
Fluoxetine + Clonazepam + Carbamazepine	10	4.4

The least frequent combination was Fluoxetine, Clonazepam, and Carbamazepine (4.4% of patients).

DISCUSSION

Many different medications are prescribed at the outpatient clinic of the Psychiatry Department at Durango General Hospital, with the SSRI's being the most common groups, followed by benzodiazepines; these groups of drugs are also reported as being the most commonly used psychiatric medications in countries like Canada and the USA (Beck et al., 2005) (Paulose-Ram et al., 2007), following the tendency to increase the use of SSRI's in psychiatry clinics (Pincus et al., 1998) (Zuvecas, 2005). These contrasts with the results from a similar study done in Germany by Bruggerman et al. in 2008 where the most common psychiatric medications were the group of the antipsychotics (Brüggermann et al., 2008), while in Trinidad, Moore et al. report the tricyclic antidepressants as the most commonly prescribed psychoactive medications (Moore et al., 2002)

A well-known phenomenon in psychoactive medication pharmacoepidemiology is the fact that the use of these drugs is increased with age and is more common in female patient (Beck et al., 2005). The data gathered in this study is consistent with those facts: more prescriptions were given to women (75%) and most medications were prescribed for the age group between 30 and 59 years of age. These results are similar to what was reported by Paulose-Ram et al. in the USA in 2007 (Paulose-Ram et al., 2007) and Beck et al. in Canada in 2005 (Beck et al., 2005)

Some epidemiology studies in Mexico have estimated a 15 to 18% prevalence of psychiatric disorders within the adult population (Caraveo-Anduaga, 1996). The National Survey of Psychiatric Disorders reports a life-long prevalence of psychiatric disorders of 28.6%, with anxiety disorders (ICD-10:F4) being the most common, followed by mental and behavioral disorders due to use of alcohol (ICD-10:F10), and affective disorders (ICD-10:F3) (Medina-Mora et al., 2003). This data is close to what was reported by Kohn et al. in 2005 about Latin America and the Caribbean (Kohn et al., 2005). Our study shows a different prevalence of psychiatric disorders, with the highest prevalence seen in anxiety disorders (ICD-10:F4), followed by affective disorders (ICD-10:F3), and then by organic mental disorders (ICD-10:F0).

One common concern with the current use of psychoactive medication for psychiatric disorders is the

problem of polypharmacy, because even in the knowledge that most guidelines suggest monotherapy as the initial step in the management of these disorders, there is a great variation in the way these medications are used[17]. In this study 76.75% of patients received more than one medication, leading to the conclusion that polypharmacy is a prevalent problem in our population, just as was reported in Germany (Brüggermann et al., 2008) in Austria (Rittmannsberger et al., 1999), and in the USA (Mojtabaiet al., 2010)

As was mentioned earlier, monotherapy is the initial step in the management of most psychiatric disorders, but this is not to say that polypharmacy or combined therapy is never required; it may be used when the patient's agitation or anxiety cannot be controlled and it poses a risk to the patient or those that surround him, or when the disorder is not under control with one medication. The most commonly used medication combinations in this study were Sertraline, Clonazepam, and Valproate (6.14%) and Fluoxetine, Clonazepam, Carbamazepine and Adepsique® (Amitriptyline, Perphenazine, and Diazepam) with a 5.26%, used for a wide variety of disorders, especially those related to anxiety and depression.

Pharmacological interactions between psychoactive medications have been studied, especially regarding new antidepressives (Hiemke et al., 2000) (Mitchell, 1997). Some reports have showed that sertraline, a SSRI, is a CYP3A4 and CYP2D6 inhibitor that has little effect on the plasma concentration of benzodiazepines and mood stabilizers when they are coadministered orally (Hemeryck et al., 2002) (Sandson et al., 2005) (Sproule et al., 1997). Regarding another commonly used combination, there has been studies showing that Carbamazepine, a mood stabilizer, increases the metabolism of benzodiazepines when they are administered simultaneously (Monaco et al., 199). Fluoxetine (SSRI) is considered a potent inhibitor of cytochrome CYP2D6 and a lower grade inhibitor of CYP3A4, so other psychoactive medication that are metabolized through this pathways may have altered plasma concentrations when administered with Fluoxetine, as is the case with tricyclic antidepressants, mood stabilizers, benzodiazepines, and antipsychotics (Hemeryck et al., 2002) (No authors listed, 2001). Other studies, such as the one by Monaco et al. published in 1999 (Monaco et al., 1999) have shown that the used of fluoxetine and carbamazepine puts the patient at increased risk for serotoninergic syndrome. Even with these data, the relationship between side effects and the previously mentioned medication combinations are not completely clear and there are clinical situations where the combinations may be required, but a strict follow up is required and sometimes drugs levels may need to be checked regularly. An observation we made was that there is not a consistent search for side effects or interactions recorded in patient files at the Durango General Hospital.

The impact of these potential interactions in adult patients with psychiatric disorders is a frequently studied topic. Some studies have suggested that the knowledge of the exact enzymatic phenotype and biotransformation pathways may result in safer prescription practices when medication combinations are used (Vandel et al., 2007). Another recommendation to try to adhere to the clinical guidelines for the most common psychiatric diseases that state, for example, that the first line therapy for anxiety and affective disorders is monotherapy with a SSRI (Ursano et al., 2004) (Howland et al., 2005) (Karas et al., 2002). The clinician may start with a low dose and titer the doses by following plasmatic drug levels (Devane, 2006), or the defined daily dose may be used to ensure therapeutic drug concentrations (The WHO, 2010).

Psychoactive medications have a relatively high security margin but may produce unwanted residual effects and benzodiazepines have dependency potential (Degner et al., 2004) (Secades-Villa et al., 2003) (Wren et al., 2003) and are prone to secondary effects, especially in elderly patients (Beck et al., 2005). To add to the matter, a study shows that almost 10,000,000 adverse reactions per year may be attributed to antipsychotics and antidepressants (Reilly et al., 2007). Seeing this, pharmacokinetic parameters, such as half-life and drug clearance, and pharmacogenetic knowledge, such as the CYP450 enzyme polymorphisms, need to be taken into account for dosage adjustments for psychoactive medications and not just base it on weight or body surface area (Seeringer et al., 2008) (Lares-Asseff et al., 2010) (Malhotra et al., 2004). By doing this, therapeutics will become more personalized, avoiding dose related complications when possible, and accounting for interpersonal variability in response to treatment (De Vane, 1998).

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