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## ORIGINAL RESEARCH

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## Off-label use of psychotropic drugs beyond officially approved indications in Colombia

*Uso de psicofármacos en indicaciones no aprobadas por la agencia regulatoria nacional de Colombia*

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### | Abstract |

**Introduction:** Off-label use of psychotropic drugs is a common practice. In Colombia, no information is available in this regard.

**Objective:** To describe off-label use of psychoactive drugs in a health promoting entity (EPS in Spanish) in Bogotá D.C.

**Materials and methods:** Cross sectional, observational study (prescription-indication), including a random sample of patients prescribed with psychotropic drugs between January and June 2010. Sociodemographic, clinical, pharmacological and concordance variables were evaluated (correlation between use indication and approved indication). Multivariate analyzes were performed looking for an association with off-label prescriptions.

**Results:** 420 evaluated patients had a mean age of 44.2±18.8 years, with female predominance (67.9%). Off-label prescription was found in 58.6-59.8% of cases. 84.3% of the prescriptions were delivered by general practitioners. The main psychoactive drugs prescribed for conditions such as tension headaches and insomnia were amitriptyline (n=128, 86.7% of off-label use), trazodone (n=93, 88.2%) and fluoxetine (n=66, 36.4%). The multivariate analysis found that being a young adult (OR=1.99, 95%CI: 1.06-3.70; p=0.030), being treated by general medicine (OR=3.40, 95%CI: 1.50-7.67; p=0.003) and being prescribed with amitriptyline (OR=11.38; 95%CI: 5.06-25.58; p<0.001) or trazodone (OR = 13.08; 95%CI: 5.23-32.68; p<0.001) increased the likelihood of receiving an off-label prescription.

**Conclusions:** Psychotropic drugs in Bogotá are used, to a great extent, as off-label in indications other than those officially approved. Thus, it is important to strengthen education and control to achieve a rational, effective and safe use of drugs.

**Keywords:** Off-Label Use; Psychotropic Drugs; Pharmacoepidemiology; Colombia (MeSH).

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### | Resumen |

**Introducción.** El uso de psicofármacos por fuera de las indicaciones aprobadas (*off-label*) es una práctica común, de la cual no se tiene información en Colombia.

**Objetivo.** Describir el uso *off-label* de psicofármacos en una entidad promotora de salud de Bogotá D.C.

**Materiales y métodos.** Estudio observacional de prescripción-indicación con una muestra aleatoria de pacientes prescritos con psicofármacos entre enero y junio de 2010. Se evaluaron variables sociodemográficas, clínicas, farmacológicas y de concordancia y se realizaron análisis multivariados buscando asociación con prescripciones no aprobadas.

**Resultados.** Los 420 pacientes evaluados tenían una edad promedio de 44.2±18.8 años, con predominio femenino (67.9%). Se encontró prescripción no aprobada en 58.6-59.8% de los casos; el 84.3% de las formulas fueron hechas por medicina general. Los principales psicofármacos en indicaciones como cefalea tensional e insomnio fueron amitriptilina (n=128; 86.7% de uso no aprobado), trazodona (n=93; 88.2%) y fluoxetina (n=66; 36.4%). En el análisis multivariado se halló que ser un adulto joven (OR=1.99; IC95%: 1.06-3.70; p=0.030), ser tratado por medicina general (OR=3.40; IC95%: 1.50-7.67; p=0.003) y ser formulado con amitriptilina (OR=11.38; IC95%: 5.06-25.58;

$p < 0.001$ ) o trazodona (OR=13.08; IC95%: 5.23-32.68;  $p < 0.001$ ) aumentan la probabilidad de recibir una prescripción no aprobada.

**Conclusiones.** En la aseguradora estudiada, los psicofármacos son utilizados en una importante proporción de indicaciones no aprobadas por las autoridades regulatorias, por lo cual es importante fortalecer la educación y el control para el empleo de los medicamentos de manera racional, efectiva y segura.

**Palabras clave:** Uso fuera de lo indicado; Psicotrópicos; Farmacoepidemiología; Colombia (DeCS).

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## Introduction

Drugs used in medical practice are effective and safe in specific indications. This is achieved through a long and rigorous study process that provides information about the specific population that can be benefited, as well as the use and appropriate dose. However, off-label use of drugs is based on the ability or freedom of physicians who prescribe them beyond approved indications when a therapeutic alternative is required.

Recently, the consumption of psychoactive drugs has increased in Colombia, which is one of the drug groups with the highest proportion of non-approved use, particularly antidepressants, antipsychotics, anxiolytics and sedatives (2-7).

Use beyond approved indications is an issue, and there is no unanimity in this regard among regulatory agencies. In fact, many of them do not even have a clear position. The US Food and Drug Administration (FDA), for example, defines off-label as the “use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling” (8).

Formulations different from the approved indication, according to a systematic review by Carton *et al.* (9) based on studies conducted around the world, show that they represent 40-75% of the total prescriptions of psychotropic drugs, mainly for mood, anxiety, insomnia and agitation disorders. Quetiapine is revealed as the main drug used off-label, especially for anxiety and insomnia. The Colombian Food and Drug Surveillance Institute (Invima in Spanish) established through Act 38 of December 13, 2006 (10) that “off-label” is a use different from that officially authorized by Invima; therefore, it refers to unauthorized use and is “only acceptable if supported by clinical studies properly conducted.”

In Colombia, little information is known on the unauthorized use of medications, and there is no clear regulation on this issue. For this reason, the following prescription-indication study is presented (11) with the purpose of describing the use of psychoactive drugs beyond the guidelines approved by the regulatory agencies in a health promoting entity (EPS) of Bogotá D.C. during the first half of 2010. It is also intended to suggest tools for the regulation and control of medications based on evidence of risk of adverse reactions, lack of effectiveness and inappropriate use of resources.

## Materials and methods

Cross-sectional study in which prescription-indication information was collected retrospectively. The sample was obtained from the

databases of drugs dispensed by Audifarma S.A. in an EPS of Bogotá D.C., as well as from the medical records of the patients included.

From a universe of 16 912 patients prescribed with a psychotropic drug for at least one month between January and June 2010, a random sample of 385 patients was classified based on the drugs to be evaluated (expected prevalence: 50%, alpha level: 5%, power: 80%) using the statistical package SPSS v22. Additionally, subjects with lower consumption requirements of diazepam, modafinil and zolpidem who were not included at first considering the classification criteria, were included later in the study, and, therefore, considered as mandatory, which increased the final size of the sample to 420 individuals.

A list of patients was obtained based on the records of Audifarma S.A. These patients were given one or more of the following psychotropic drugs: valproic acid, alprazolam, amitriptyline, bromazepam, carbamazepine, chlorpromazine, clozapine, diazepam, divalproate, fluoxetine, gabapentin, haloperidol, lamotrigine, lithium, methylphenidate, midazolam, modafinil, olanzapine, oxcarbazepine, pregabalin, risperidone, sertraline, trazodone, venlafaxine and zolpidem. During the same period, a chemist reviewed the medical records to know the medical reason for the prescription. When the drugs with the highest amount of prescriptions were determined, a bibliographical search of the clinical and academic support was made for the different unapproved indications that were found (12).

For the study the following variables were taken into account, and were recorded in a Microsoft Excel database:

*Sociodemographic:* age (infants <14 years, adolescents 14-18 years, young adults 19-45 years, and adults >45 years) and sex.

*Clinical:* diagnosis and indication for prescription.

*Pharmacological:* name of prescribed medication, route of administration, posology, pharmaceutical form and specialty of the prescribing physician.

*Concordance:* correlation between the use indication of the psychoactive drug and the indication approved by Invima and FDA (indication, dose, route of administration, contraindications).

Finally, each prescription was classified as a) *off-label*: use other than the approved by the regulatory agency; b) *approved use*: use under approved conditions; c) *no report*: use is not specified in the medical record, and d) *not evaluable*: no information that supports the use of the psychoactive drug and impossibility to evaluate whether the prescription is appropriate or not (this option was only applied for mandatory inclusion drugs because of the impossibility of replacing the information).

This study met the specifications of the category “research without risk” according to Resolution 8430 of 1993 of the Ministry of Health of Colombia (13), which establishes the scientific, technical and administrative standards for health research. The principles of beneficence and confidentiality of patients were preserved as established by the Declaration of Helsinki.

## Analysis plan

Data were analyzed using the statistical package SPSS Statistics version 22.0 for Windows (IBM, U.S.A.). A description of frequencies and proportions was made for categorical variables, and central tendency and dispersion measures for continuous variables. Chi-square tests were used for comparing categorical variables, using a variable dependent on off-label use of a drug. Binary logistic regression models were used based on the prescription not

approved by Invima as a dependent variable (because it was of greater local interest), and  $p < 0.05$  was determined as the level of statistical significance.

## Results

420 clinical histories of patients prescribed with psychoactive drugs in Bogotá D.C. were evaluated. The mean age was  $44.2 \pm 18.8$ , and distribution was obtained with a female predominance of 67.9%.

Table 1 shows the distribution by sex, age group, specialty of the prescribing physician and method of use, as well as the proportion of off-label use.

**Table 1.** Socio-demographic variables, prescribing physician and off-label indications of psychoactive drugs in patients affiliated with a health promoting entity. Bogotá D.C. 2010.

Variables		n=420	(%)	Off-label use proportion	
				Invima %	FDA %
Sex	Male	135	32.1	50.4	53.3
	Female	285	67.9	62.5	62.8
Age group	Infants (<14 years)	20	4.8	10.0	15.0
	Adolescents (14-18 years)	35	8.3	48.6	45.7
	Young adult (19-45 years)	179	42.6	69.8	70.9
	Adult (>45 years)	186	44.3	54.8	56.5
Prescribing physician	General practitioner	355	84.3	62.8	63.9
	Neurology	15	3.6	40.0	40.0
	Psychiatry	12	2.9	8.3	25.0
General results of use	Off-label use			58.6	59.8
	Approved use			31.0	29.8
	No report			7.4	7.4
	Not evaluable			3.1	3.1

Source: Own elaboration based on data obtained in the study.

It was not possible to describe the use of drugs by route of administration different from that recommended by the health agency, because 31.4% of prescriptions did not report this variable for each psychoactive drug.

Table 2 lists the seven most frequent formulations of psychotropic drugs, and details the proportion of off-label prescriptions and the diagnostic reasons for off-label use.

## Bivariate analysis

When comparing the dependent variable “off-label prescription not approved by Invima”, the variables *prescribing a psychoactive drug as a painkiller* and *being treated for headache with psychoactive drugs* were found to be the most likely reasons for off-label indications. However, other variables such as prescription of amitriptyline or trazodone, receiving psychotropic drugs for migraine, being a young adult, and being formulated by general practitioners increased the probability of off-label prescriptions. Interestingly, the total number of patients treated for pain management ( $p=0.0001$ ) and insomnia ( $p=0.0001$ ) with psychotropic drugs were prescribed with drugs based on off-label indications.

It was also found that *the use of psychoactive drugs for the treatment of epilepsy* and *being treated by psychiatry* were the variables that further reduced the risk of unapproved use, although, prescription with

fluoxetine or carbamazepine, depression and schizophrenia, being male and being an infant were associated with a lower probability of using psychoactive drugs with an off-label indication.

Table 3 presents the associated variables in relation to the decrease or increase of the risk of prescribing off-label indications of drugs.

**Table 2.** Psychopharmaceuticals most commonly used in off-label indications in patients affiliated with a health promoting entity. Bogotá D.C. 2010.

Drug	n	Invima %	Main off-label indications	FDA %	Main off-label indications
Amitriptyline	128	86.7	Tension headache	87.5	Tension headache
			Insomnia		Insomnia
Trazodone	93	88.2	Tension headache	88.2	Tension headache
			Insomnia		Insomnia
Fluoxetine	66	36.4	Other anxiety disorders	36.4	Other anxiety disorders
			Migraine without aura		Migraine without aura
Carbamazepine	30	13.3	Sleep disorders	16.7	Sleep disorders
			Myalgia		Myalgia
Valproic acid	28	3.6	Schizophrenia	3.6	Schizophrenia
Diazepam	23	43.5	Essential tremor	39.1	Essential tremor
			Myoclonus		Benign paroxysmal vertigo
Zolpidem	11	9.1	Depressive episode	9.1	Depressive episode

Invima: Food and Drug Surveillance Institute; FDA: Food and Drug Administration.

Source: Own elaboration based on data obtained in the study.

**Table 3.** Bivariate analysis of the variables associated with off-label prescription of psychotropic drugs in patients affiliated with a health promoting entity. Bogotá D.C. 2010.

Associated variable		OR	95%CI	p
Protective factors of use in approved indication	Being treated by psychiatry	0.06	0.08-0.47	<0.001
	Treatment with fluoxetine	0.34	0.19-0.58	<0.001
	Treatment with carbamazepine	0.12	0.04-0.33	<0.001
	Being used for epilepsy	0.02	0.006-0.09	<0.001
	Being used for depression	0.22	0.13-0.38	<0.001
	Being used for schizophrenia	0.22	0.13-0.38	<0.001
Risk factors of use in approved indication	Treatment with amitriptyline	7.59	4.33-13.29	<0.001
	Treatment with trazodone	7.40	3.80-14.41	<0.001
	Being used as a painkiller	41.9	5.72-307.04	<0.001
	Being used for headaches	23.6	5.67-98.36	<0.001
	Being used for migraine	6.44	1.91-21.71	0.001
	Adult (19-45 years)	2.29	1.52-3.44	<0.001
	Being treated by a general practitioner	3.08	1.77-5.35	<0.001

Source: Own elaboration based on data obtained in the study.

## Multivariate analysis

By including the associated variables in a statistically significant manner, a binary logistic regression was performed. It is presented in

Table 4, with the variables that were statistically associated with a higher risk of off-label prescriptions according to the approval of Invima.

**Table 4.** Multivariate analysis of the variables associated with off-label prescription of psychotropic drugs in patients affiliated with a health promoting entity. Bogotá D.C. 2010.

Variables	B	SE	Wald	DF	Sig	OR	95%CI	
							Lower	Higher
Young adult	0.688	0.317	4.717	1.000	0.030	1.990	1.069	3.703
Being treated by a general practitioner	1.224	0.415	8.682	1.000	0.003	3.401	1.507	7.677
Treatment with amitriptyline	2.432	0.413	34.611	1.000	<0.001	11.380	5.062	25.585
Treatment with trazodone	2.571	0.467	30.276	1.000	<0.001	13.080	5.234	32.685
Headache	2.057	0.851	5.848	1.000	0.016	7.823	1.477	41.446
Epilepsy	-2.720	0.829	10.765	1.000	0.001	0.066	0.013	0.334
Depression	-1.743	0.383	20.674	1.000	<0.001	0.175	0.083	0.371

B: Regression coefficient; SE: standard error; DF: degree of freedom; Sig: level of significance.

Source: Own elaboration based on data obtained in the study.

## Discussion

This study served to identify the most common use of psychoactive drugs used beyond the approval of regulatory agencies and the FDA, as well as the diagnostic reasons, the prescriptive specialty and the variables associated with this practice in an EPS of Bogotá D.C. This contribution is the first approach to information regarding the unapproved use of psychotropic drugs in Colombia.

The proportion of psychoactive drugs found in this study (58.6%), especially antidepressants in non-approved indications, is within the range published by other authors such as Kharadi *et al.* (14) (39.5%, predominantly benzodiazepines), Leslie *et al.* (7) (60.2%) and Chen *et al.* (15) (75.4% predominantly antidepressants).

As presented in the systematic review of Carton *et al.* (9), off-label prescriptions correspond to 40-75% of total prescriptions of psychotropic drugs worldwide according to the reviewed studies, which coincides with the data presented in this study. In this review, the most frequent uses of off-label medications are mood, anxiety and insomnia disorders. However, this research showed that they were almost always used for the management of tension headache and insomnia, being amitriptyline and trazodone the most used drugs, compared with quetiapine as the main drug in this systematic review (9). These differences may be explained by the access to medicines in the Colombian health system, where the prescription of many of these psychotropic drugs is restricted, although amitriptyline and trazodone are over-the-counter.

Off-label drug use may be justified in cases that require therapeutic alternatives, for example, in population groups with few investigations such as infants or pregnant women (1). However, statistical analyzes show that these prescriptions were more frequent in young adults, which may be related to the lack of knowledge by the general practitioner of the indications authorized for the drugs, the population that uses these type of drugs, and those easily related to diagnoses with other approved alternatives (1,2,8).

This scenario leads to reflect on whether the physician, when prescribing, makes an appropriate analysis of the risk-benefit balance based on available clinical evidence and on the Invima guidelines that

establish that unauthorized use is acceptable only if it is supported by adequate clinical studies (10).

Amitriptyline and trazodone were frequently prescribed off-label to treat tension headache and insomnia. Regarding amitriptyline, some studies have reported its effectiveness in these two indications (14-17); however, regulatory agencies still do not approve these uses. Something similar occurs with trazodone when indicated to treat sleep disorders. Some reports show good results, but it has not been approved for it yet.

This situation creates a gap between the clinical practice guidelines that include it, and the surveillance and regulation measures that have not been updated. As a consequence, the responsibility of prescribing falls directly on physicians without the support of the drug regulatory agencies (17,18).

Amitriptyline, trazodone, fluoxetine, carbamazepine and valproic acid are less likely to be used without following the guidelines in patients with depression or epilepsy, but may increase the likelihood of unapproved use in different indications, although they may be effective (16,18).

Given the results presented in this paper, questions are raised about the relevance of unapproved prescriptions, since the panorama of off-label drug use does not offer conclusive answers. Perhaps, the best approach to a more rational use of drugs is based on the availability of resources —drugs and other technologies—, the robustness and availability of scientific evidence, the expertise of the physician, and the competence of the surveillance authorities (1).

Therefore, the efforts of all health professionals, regulatory agencies and the pharmaceutical industry should be focused on working together to ensure patient safety, the collection of scientific evidence and an informed prescription. This translates into a more rational use of drugs (16,17).

One of the limitations of this work is its results, which were obtained from a single health promoting institution and can be extrapolated to populations with similar characteristics. In addition, the information was collected from the clinical records and the drug dispensing database, but not through interviews with physicians who are the actual decision makers and are responsible of selecting the



most appropriate therapy for their patients. However, the rigor of data collection allows us approach the reality of the use of psychoactive drugs in indications not authorized by regulatory agencies.

In conclusion, psychoactive drugs, especially antidepressants and antiepileptics, are used in this cohort of patients in a high proportion in indications not approved by regulatory agencies such as Invima and FDA, and were mostly prescribed by general practitioners for treating headaches and insomnia. It is important to strengthen information and continuing education programs, as well as relevant updates of health records of some psychotropic drugs with precise indications that already have sufficient evidence. Similarly, surveillance and control strategies should be developed for these drugs or included in pharmacovigilance programs by regulatory agencies when their uses may compromise patient safety in order to minimize the risks related to incomplete or inadequate information that may lead to increased off-label use of medications (18).

### Conflict of interest

None stated by the authors.

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