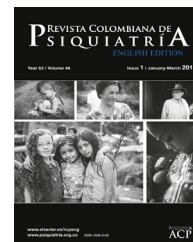




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Original article

For what indications are antidepressants being used in adults in Colombia?



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ABSTRACT

Introduction: Antidepressants are useful in the pharmacological treatment of different depressive and anxiety disorders, as well as being potentially useful in other indications. The aim of the study was to determine the indications for which antidepressants are being prescribed in patients over 18 years of age registered with the Colombian Health System.

Methods: Retrospective study with data from patients over 18 years old, of either sex, registered with the Colombian Health System, who are prescribed antidepressants. Medical records were reviewed, looking for indications approved and not approved by regulatory agencies. Patients were identified randomly, as well as the sociodemographic, clinical and pharmacological variables that could be associated with prescriptions for unapproved indications.

Results: 351 patients were evaluated, with a mean age of 60.4 ± 15.3 years, of whom 72.6% were women. They were attended in 34 cities, with prescriptions mainly by general practitioners ($n = 276$; 78.6%), and psychiatrists ($n = 42$; 12.0%). Selective serotonin reuptake inhibitors were the most widely prescribed antidepressants ($n = 204$; 58.1%), followed by atypicals ($n = 76$; 21.7%). The most frequent indications were for depression ($n = 169$; 48.1%), anxiety ($n = 48$; 13.7%), pain ($n = 22$; 6.3%) and sleep disorders ($n = 17$; 4.8%). A total of 188 prescriptions (53.6%) were made for approved indications, and the remaining 163 (46.4%) were classified as unapproved.

Conclusions: Antidepressants are being prescribed for the treatment of depression, anxiety, pain and sleep disorders, especially in older adult women, but almost half of the formulations were for unapproved indications.

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Para qué indicaciones se están utilizando los antidepresivos en adultos de Colombia

R E S U M E N

Palabras clave:

Antidepresivos
Indicación no aprobada
Depresión
Trastornos de ansiedad
Farmacoepidemiología

Introducción: Los antidepresivos son útiles en el tratamiento farmacológico de diferentes trastornos depresivos y de ansiedad, además de su potencial utilidad para otras indicaciones. El objetivo del estudio es determinar las indicaciones para las que se están prescribiendo los antidepresivos a pacientes mayores de 18 años afiliados al Sistema de Salud de Colombia.

Métodos: Estudio retrospectivo con datos de pacientes mayores de 18 años, de cualquier sexo, afiliados al Sistema de Salud de Colombia, a los que se prescriben antidepresivos; se revisaron las historias clínicas buscando indicaciones aprobadas y no aprobadas por agencias reguladoras. Se identificó a los pacientes aleatoriamente, así como las variables sociodemográficas, clínicas y farmacológicas que se pudieran asociar con prescripciones para indicaciones no aprobadas.

Resultados: Se evaluó a 351 pacientes, con una media de edad de $60,4 \pm 15,3$ años; el 72,6% eran mujeres; se atendieron en 34 ciudades, y los prescriptores principalmente fueron médico general ($n = 276$; 78,6%) y psiquiatra ($n = 42$; 12,0%). Los inhibidores selectivos de la recaptación de serotonina fueron los antidepresivos más prescritos ($n = 204$; 58,1%), seguidos de los atípicos ($n = 76$; 21,7%). Las indicaciones más frecuentes fueron depresión ($n = 169$; 48,1%), ansiedad ($n = 48$; 13,7%), dolor ($n = 22$; 6,3%) y trastornos del sueño ($n = 17$; 4,8%). Un total de 188 prescripciones (53,6%) se hicieron para indicaciones aprobadas y las 163 (46,4%) restantes se catalogaron como no aprobadas.

Conclusiones: Los antidepresivos se están prescribiendo para tratar depresión, ansiedad, analgesia y trastornos del sueño, especialmente a mujeres adultas mayores, pero casi la mitad de las formulaciones fueron para indicaciones no aprobadas.

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Introduction

Antidepressant medicines are useful in drug treatment for various depressive disorders and anxiety disorders, in addition to being potentially useful in chronic pain, peripheral neuropathy, fibromyalgia and other indications^{1–4}. This group of medicines comprises a wide array of drugs, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and atypical antidepressants⁵.

Prescribing antidepressants for indications not approved by regulatory agencies (*off label*)⁶ is promoted by the publication of studies with positive results in conditions other than those under which these drugs were originally studied. This may incite physicians to use them if the potential benefits outweigh the risks, as documented in nearly half of prescriptions in this drug group^{7,8}, which has led to their use in conditions in which their efficacy and safety have not yet been thoroughly determined⁹.

Frequent use of antidepressants, especially SSRIs and atypical antidepressants¹⁰, has been identified in the adolescent population at high rates (42.9%) outside their approved indications in Colombia¹¹, especially given the potential risks of these medicines^{1,12}, and in particular the high anticholinergic load of tricyclic antidepressants and some atypical

antidepressants, which increase the likelihood of older adults experiencing instability, falls, fractures, delirium and even cognitive decline^{13,14}. Hence the objective of this study was to determine the indications for which antidepressants are being prescribed to patients over 18 years of age enrolled in the Colombian Health System.

Methods

This retrospective study included data from patients over 18 years of age, of either sex, affiliated with an insurer (health-promoting entity [HPE]) for the contribution-based healthcare system of the Colombian Health System, seen in a medical appointment between 1 August 2015 and 31 July 2016, who were taking at least one antidepressant, in different cities selected by convenience, since pertinent and reliable databases were available for them.

From all patients ($n = 3.669$) continuously taking at least one prescription antidepressant during the observation period, simple random sampling was done, with 5.0% permissible error and 80% power, yielding a study sample of 351 patients.

A trained physician was in charge of collecting data from the medical records of each randomly selected patient; the information was reviewed and validated by a pharmacologist. The following groups of variables were collected:

Table 1 – Groups of antidepressants and medicines by approved and off-label indications according to the FDA.

Group	Medicine	Indications	
		Approved	Off-label
Tricyclic antidepressants	Amitriptyline	Depression	Fibromyalgia, functional dyspepsia, tension headache (prophylaxis), irritable bowel syndrome, migraine prophylaxis, chronic neuropathic pain, post-herpetic neuralgia, sialorrhoea
	Imipramine	Major depression (unipolar)	Bulimia nervosa, neuropathic pain, panic disorder
	Fluoxetine	Major depression (unipolar), obsessive compulsive disorder, panic disorder, bulimia nervosa	Fibromyalgia, generalised anxiety disorder, post-traumatic stress disorder, body dysmorphic disorder
SSRIs	Sertraline	Major depression (unipolar), post-traumatic stress disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder	Generalised anxiety disorder, bulimia nervosa, premature ejaculation, body dysmorphic disorder
	Escitalopram	Major depression (unipolar), generalised anxiety disorder	Obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, premature ejaculation, bulimia nervosa
	Paroxetine	Generalised anxiety disorder, major depression (unipolar), obsessive compulsive disorder, panic disorder, social anxiety disorder	Premature ejaculation, body dysmorphic disorder
	Fluvoxamine	Obsessive compulsive disorder	Major depression (unipolar), panic disorder, bulimia nervosa, social anxiety disorder, post-traumatic stress disorder
SNRIs	Duloxetine	Fibromyalgia, generalised anxiety disorder, major depression (unipolar), chronic joint pain (lumbago), neuropathic pain	Chemotherapy-induced peripheral neuropathy
	Venlafaxine	Generalised anxiety disorder, major depression (unipolar), panic disorder, social anxiety disorder	Post-traumatic stress disorder, neuropathic pain, narcolepsy, migraine prevention
Atypical antidepressants	Bupropion	Major depression (unipolar), smoking cessation	Attention deficit/hyperactivity disorder, bipolar depression
	Trazodone	Unipolar major depression (alternative)	Insomnia (alternative), aggressiveness or agitated behaviour associated with dementia
	Mirtazapine	Major depression (unipolar)	Prophylaxis for tension headache, panic disorder

- 1 Sociodemographic characteristics: age (years), sex and city of residence.
- 2 Clinical characteristics: diagnosis inciting antidepressant use.
- 3 Antidepressant medicines by group: the drugs used, classified as tricyclic antidepressants (amitriptyline, imipramine, etc.), SSRIs (sertraline, fluoxetine, etc.), SNRIs (duloxetine, etc.), atypical antidepressants (trazodone, bupropion, etc.), as well as dose and dosing range; defined daily dose (DDD) was taken as a unit of measure to compare doses used to recommended doses and have a parameter for comparison to similar studies.
- 4 Comorbidities: a) diabetes mellitus; b) hypertension; c) cardiac arrhythmias; d) bipolar disorder; e) sleep disorders; f) schizophrenia; g) attention deficit disorder; h) hypothyroidism; i) cancer; j) other diagnoses recorded in medical records.

Indications were established based on whether they were approved or off label according to the United States Food and Drug Administration (FDA) for the adult population. Table 1 shows groups, medicines and indications.

The study was approved by the Bioethics Committee of the Universidad Tecnológica de Pereira [Pereira Technological University], in the risk-free research category, and the principles established by the Declaration of Helsinki were respected. Medical records were accessed remotely with institutional permission from the HPE and the Bioethics Committee. Patients' personal data were not used.

Analysis plan

Information was analysed using the SPSS Statistics statistics software package, version 24.0 for Windows (IBM, United States). Descriptive statistics were used including measures of central tendency, position and dispersion depending on the normality behaviour of the continuous variables (Kolmogorov-Smirnov test), in addition to frequencies and proportions for categorical variables. Student's t-test and analysis of variance (ANOVA) were used to compare quantitative variables, and the χ^2 test was used to compare categorical variables. Binary logistic regression models were applied to identify variables associated with off-label antidepressant use.

Table 2 – Prescribing patterns and approved and off-label indications for antidepressants in the adult population enrolled in the Colombian Health System.

	n	%	Mean dose (mg/day)	Mode	nDDD	Women, %	Age (years) ^a	Most common approved indication	Most common off-label indication
SSRIs									
Fluoxetine	101	28.8	19.7	20	0.98	76.0	58.6 ± 12.4	Depression	Chronic pain
Sertraline	68	19.4	58.2	50	1.16	68.9	60.6 ± 16.9	Depression	No other indications recorded by physician
Escitalopram	40	11.4	17.3	20	1.73	78.4	55.5 ± 15.3	Depression	Post-traumatic stress disorder
Paroxetine	12	3.4	20	20	1	90.9	56.6 ± 19.4	Depression	No other indications recorded by physician
Fluvoxamine	6	1.7	100	100	1	33.3	45.3 ± 14.2	Anxiety	Depression
SNRIs									
Duloxetine	22	6.3	45	60	0.75	90	54.3 ± 10.9	Depression	No other indications recorded by physician
Venlafaxine	14	4.0	115.3	150	1.15	69.2	63.7 ± 12.2	Depression	Dementia
Tricyclic antidepressants									
Amitriptyline	35	10.0	25.15	25	0.33	68.7	64.8 ± 14.2	Depression	Chronic pain
Imipramine	13	3.7	25	25	0.25	91.7	58.7 ± 13.5	Depression	Chronic pain
Atypical antidepressants									
Bupropion	8	2.3	225	300	0.75	66.6	43.5 ± 14.1	Depression	Generalised anxiety disorder
Trazodone	95	27.1	52.1	50	0.17	66.6	66.7 ± 15.5	Depression	Insomnia
Mirtazapine	11	3.1	27.5	30	0.91	50	63.0 ± 14.4	Depression	No other indications recorded by physician
nDDD: mean dose-to-defined daily dose ratio; SNRIs: serotonin–norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors.									
^a Mean ± standard deviation.									

A *p* value <0.05 was set as a threshold for statistical significance.

Results

Those evaluated were 351 patients with a prescription for antidepressants (mean age 60.4 ± 15.3 years), with a marked predominance of women ($n=255$; 72.6%), seen primarily in the cities of Manizales ($n=86$; 24.5%), Bucaramanga ($n=46$; 13.1%), Pereira ($n=32$; 9.1%), Ibagué ($n=28$; 8.0%), Cartagena ($n=24$; 6.8%), Barranquilla ($n=23$; 6.6%), Medellín ($n=21$; 6.0%) and 27 other cities. Antidepressants were prescribed in most cases by general practitioners ($n=276$; 78.6%), followed by psychiatrists ($n=42$; 12.0%), family physicians ($n=15$; 4.3%), internists ($n=13$; 3.7%) and neurologists ($n=2$; 0.6%).

SSRIs were the most commonly prescribed antidepressants ($n=204$; 58.1%), followed by atypical antidepressants ($n=76$; 21.7%) and tricyclic antidepressants ($n=44$; 12.5%). Table 2 shows prescribing patterns for different prescribed antidepressants, with frequency of indication, dose, DDD ratio and sex distribution. It was found that 19.9% ($n=70$) of prescriptions were made in combination treatment with antidepressants, primarily for depression ($n=46$; 13.1%), anxiety ($n=7$; 2.0%), neuropathic pain or fibromyalgia ($n=4$; 1.1%), among others. The most common combinations of antidepressants were: fluoxetine + trazodone ($n=20$; 5.7%), sertraline + trazodone ($n=14$; 4.0%) and escitalopram + trazodone ($n=7$; 2.0%).

The most common indications were: depression ($n=169$; 48.1%), anxiety ($n=48$; 13.7%), analgesia ($n=22$; 6.3%), sleep disorders ($n=17$; 4.8%), bipolar disorder ($n=9$; 2.6%), fibromyalgia ($n=6$; 1.7%) and 11 other diagnoses for the 25 remaining patients (7.3%). In 55 cases (15.7%), the indication for the prescription was not identified in the medical record, and three patients (0.9%) had records of a history of attempting suicide.

A total of 188 prescriptions (53.6%) were made for FDA-approved indications; the other 163 (46.4%) were classified as off label. Table 2 shows the medicines and the most common indications for each one. Most prescriptions for antidepressants with an FDA-approved indication were found in patients 45–64 years of age ($n=90$, 25.6%), followed by patients 65 years of age or older ($n=67$, 19.1%).

The most common comorbidities were hypertension ($n=196$; 55.8%), hypothyroidism ($n=80$; 22.8%), dyslipidaemia ($n=74$; 21%), diabetes mellitus ($n=67$; 19.1%) and sleep disorders ($n=42$; 11.9%).

Multivariate analysis

Binary logistic regression to identify variables associated with off-label antidepressant prescription found that patients treated in the city of Manizales were less likely to take them for off-label indications, while patients on combination treatment or with a prescription from a psychiatrist were more likely to do so (Table 3).

Table 3 – Multivariate analysis of the variables associated with prescribing antidepressants in off-label indications for adults enrolled in the Colombian Health System.

Variable	<i>p</i>	OR (95% CI)
Woman	0.07	1.65 (0.96–2.846)
Age		
18–30 years	0.245	Ref.
30–45 years	0.098	0.20 (0.03–1.347)
45–65 years	0.235	0.33 (0.055–2.042)
>65 years	0.135	0.24 (0.038–1.555)
Combination treatment with 2 antidepressants	0.001	2.83 (1.507–5.316)
Hypertension	0.082	0.62 (0.36–1.063)
Treated in Manizales	0.005	0.43 (0.237–0.768)
Treated in Medellín	0.155	2.89 (0.669–12.53)
Prescription by a psychiatrist	0.023	2.66 (1.145–6.185)

95% CI: 95% confidence interval; OR: odds ratio.

Discussion

This study managed to identify, in real-world clinical practice, the main indications for antidepressants in different cities in Colombia, including the most commonly prescribed groups, doses, comorbidities and use for off-label indications.

Mean age at the time of having antidepressants prescribed was 60 years, paralleling findings in other studies in the general population¹⁰, with older adults using them most often. This was consistent with higher rates of depression and anxiety in the latest years of life, which may be linked to concomitant diseases and ageing-related conditions. In addition, drug treatment in this age group is more difficult, as they take more medications for their comorbidities, leading to polypharmacy and a heightened risk of side effects^{13,15}. Therefore, antidepressants should be prescribed with caution in this population with a preference for the most selective ones¹⁰.

Depression and most anxiety disorders more commonly affect women (59.0%–72.6% in this report), as shown in other studies in Colombia, Spain and the United States; this has been linked to gender discrimination and exposure to sexual abuse in childhood and adulthood, among other things, in addition to other disorders for which antidepressants are used more often in women^{10,11,16,17}.

Various studies in Colombia and elsewhere have shown that SSRIs, especially fluoxetine, are the most commonly used antidepressants^{10,11,15,16,18}. Indeed, a Cochrane review found that fluoxetine was better tolerated than other SSRIs (venlafaxine and sertraline) and tricyclic antidepressants. This situation is to be expected in Colombia, as fluoxetine is one of the antidepressants in the manual of medicines included in the health system's benefits plan and it is backed by good evidence for multiple indications^{10,11,16}.

Depression and anxiety disorders are the conditions for which antidepressants were most commonly prescribed in this study; however, indications that lacked the support of regulatory agencies such as the FDA, were often seen; in this instance, such indications accounted for nearly 50% of cases

— far from the figure for adolescents in Colombia (23.4% of patients were taking them for off-label indications)¹¹. In studies conducted in the United States, such as a study published by Vijay et al., the proportion of off-label indications for antidepressants was 12.9%, and the main ones were for SSRIs to treat psychosis in bipolar patients and for trazodone to treat insomnia; this was also a common finding in this study. It is interesting to note that both Vijay et al.'s study and this one found that prescription of antidepressants by psychiatry increased the likelihood of said prescription being for off-label indications. This could be accounted for by the greater complexity and the different diagnoses that this specialisation must treat or greater exposure to drug advertising^{8,19}.

Of particular note is their use to treat pain, especially neuropathic pain, which was seen in 6.3% of patients in this report, where amitriptyline and duloxetine were often prescribed for this indication, although the former was more commonly associated with side effects, in particular anticholinergic ones. This has promoted administration of dual antidepressants, which have shown evidence of effectiveness against neuropathic pain, some with approved and others with off-label indications^{20,21}.

In the multivariate analysis, off-label indications were associated with combination treatment with antidepressants. The clinical practice guidelines do not recommend this, as it is not approved and benefits have not been established in robust clinical trials for indications such as anxiety or depression. However, for patients with severe, resistant depression, two antidepressants with different mechanisms of action can be combined^{22,23}. On combination treatment, patients are exposed to a practice without confirmed benefits and with potential for more adverse reactions. However, to treat pain in fibromyalgia, some evaluations from the Cochrane collaboration have shown that combining antidepressants could lead to greater improvement with single-drug treatment, especially in patients with difficult-to-manage conditions²⁴.

Sleep disorders are an increasingly common reason for consultation as they affect the quality of life of patients and their families²⁵ and lead to prescription of at least one medicine. For example, in this study, nearly 5% of indications for antidepressants were linked to sleep disorders, especially trazodone, which, in addition to being recommended to treat depression, could have benefits for anxiety and insomnia²⁶⁻²⁸. In addition, a study by Schwasinger-Schmidt et al. found in the United States that trazodone was more often prescribed for insomnia than for depression, in an indication considered off label²⁶, primarily because it causes adverse effects such as drowsiness, weight gain and motor instability, rendering this group of patients (with a mean age of 60 years) more vulnerable to falls with hip fractures, with the serious implications that this entails^{14,26,27}.

This analysis had certain limitations particular to observational studies, such as an inability to identify patients who had acquired antidepressants outside the health system, whether they were really taking them and what adverse effects they really experienced, as well as a possible lack of information supplied in medical records, especially in relation to suicidal ideation and suicide attempts. Furthermore, due to logistical difficulties with the Colombian health system, some of

these medicines were only covered for certain specific indications, inciting physicians to change diagnoses in prescribing records to ensure treatment access with no need for a special rationale during formulation. In addition, only patients from a contribution-based or single-insurer payment healthcare system were included, such that patients with other insurers and patients from a subsidised healthcare system were excluded. However, the study had strengths such as its rigorous search for clinical information and drug supply, which made it possible to determine whether patients were receiving medicines effectively.

Conclusions

With these results, it can be concluded that antidepressants were being prescribed in particular to women with a mean age of 60 years for depression, anxiety, analgesia and sleep disorders, but nearly half of indications were off label. These findings may be of use to clinicians, the Colombian regulatory agency for medicines, scientific associations and decision-makers. Nevertheless, further studies are needed to evaluate the effectiveness of those drugs for the indications for which they are used.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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