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ORIGINAL ARTICLE

Antidepressant use and off-label prescribing in primary care in Spain (2013–2018)

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KEYWORDS
Pharmacoepidemiology;
Drug utilization;
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Abstract
Introduction: Recent studies show an increase in the use of antidepressants in minors (younger than 18 years), although few antidepressants are indicated for this age group. The aim of our study was to calculate the annual prevalence of antidepressant use in children and adolescents and to review the adherence of prescription to current indications.
Methods: Study of the prevalence of antidepressant use in minors based on the records of the Electronic Database for Pharmacoepidemiologic Studies in Primary Care (BIFAP) of Spain for the 2013–2018 period, considering at least one prescription per year for each patient.
Results: The prevalence of antidepressant prescription in patients from the BIFAP cohort increased between 2013 (7.97 prescriptions per 1000 patients) and 2018 (8.87 prescriptions per 1000 patients), in most groups and in both sexes. In this period, female patients received the most prescriptions, surpassing prescriptions in male patients by up to 2.5 points in the overall rates. In patients younger than 13 years, this trend was inverted and antidepressant use was higher in male patients. The prevalence of prescription rose with increasing patient age, as did the proportion of off-label prescriptions. The use of off-label medication decreased over time.
Conclusions: There was a gradual increase in the prevalence of antidepressant prescription in minors younger than 18 years, with a predominance of the female sex. The high proportion of unapproved medication use in this age group calls for more thorough investigation of the risk-benefit balance of these treatments and of safer treatment alternatives.

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PALABRAS CLAVE
Farmacoepidemiología;
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Antidepresivos;
Uso fuera de ficha técnica;
Registro médico computarizado

Utilización de antidepresivos y prescripción fuera de ficha técnica en atención primaria en España (2013−2018)

Resumen
Introducción: Estudios recientes muestran un aumento del uso de antidepresivos en menores de 18 años aunque pocos de ellos cuentan con indicación en este grupo de edad. El objetivo de este estudio es calcular la prevalencia anual del uso de antidepresivos en niños y adolescentes y revisar la adecuación de la prescripción a las indicaciones actuales.
Métodos: Estudio de prevalencia de la utilización de antidepresivos en menores de 18 años a partir de los registros de la Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP) durante el periodo 2013−2018, considerando al menos una prescripción por año para un mismo paciente.
Resultados: La prevalencia de prescripción de antidepresivos entre los pacientes de la cohorte BIFAP ha aumentado de 2013 (7,97 prescripciones/1000 pacientes) a 2018 (8,87 prescripciones/1000 pacientes) en la mayoría de los grupos y en ambos sexos. El sexo femenino suma la mayoría de las prescripciones, superando al masculino en hasta 2,5 puntos en las tasas generales. En menores de 13 años la tendencia se invierte y los antidepresivos predominan en los chicos. La prevalencia de las prescripciones aumenta con la edad de los pacientes, igual que la proporción de tratamientos fuera de ficha técnica. El empleo de fármacos sin indicación disminuye con el transcurso del tiempo.
Conclusiones: Observamos un aumento gradual en la prevalencia de prescripción de antidepresivos en menores de 18 años, preponderante en el sexo femenino. La elevada proporción de uso de estos fármacos sin indicación autorizada, exige profundizar en el balance beneficio-riesgo y en alternativas de tratamiento más seguras.

Introduction

Recent studies have evinced increases in the use of antidepressant drugs in children and adolescents in the past few years.[1–4] These drugs were developed for use in adults, and few are indicated for treatment in these age groups.[5]

At present, only 7 antidepressants are indicated for use in individuals under 18 years in Spain. Each of them was authorised for use under very specific conditions and starting from a specific age.[1,6] It is important to keep in mind that while the number of trials of antidepressant drugs in children and adolescents has been increasing, off-label prescriptions are still being made and are often associated with an increase in adverse events because safe dosage ranges and contraindications have yet to be established.[7–9] While off-label use is frequent in the paediatric age group, the Committee on Medicines of the Asociación Española de Pediatría (Spanish Association of Pediatrics) has underscored the need to improve the information available on medicines used in this population.[10]

In addition to the adverse reactions and side effects that antidepressants may trigger,[11] it is important to consider the potential risk of suicidal behaviour associated with their use.[11–15] The increasing reluctance worldwide to use antidepressants at these ages has motivated the performance of a review by the Committee on Medicines Used in Humans to assess the risk-benefit ratio of antidepressant use in the paediatric population.[16] Its results showed that these drugs should not be used in children and adolescent outside the specific authorised indications, and in the sporadic cases in which physicians may choose to initiate treatment with one, the patient should be closely monitored.

Due to all of the above, it is important to know the current situation of antidepressant prescribing in children and adolescents. The aim of our study was to estimate the annual prevalence of antidepressant use in children and adolescents from 2013 to 2018 and to determine temporal trends during this period, in addition to assessing the appropriateness of prescribing based on current indications.

Material and methods

We conducted a retrospective observational study of antidepressant prescriptions made to individuals aged less than 18 years from January 1, 2013 to December 31, 2018 through the electronic records held in the primary care pharmacological surveillance database of Spain (BIFAP: http://www.bifap.org),[17] which has data on nearly 12 million patients in 10 autonomous communities in Spain updated since 2001. This study was conducted in the framework of the ANSIONIA project (pharmacological epi-

demiology of anti-anxiety and antidepressant treatment in children and adolescents), authorised by the Agencia Española de Medicamentos y productos Sanitarios (AEMPS, Spanish Agency of Medicines and Medical Devices) under file DPS-ANS-2019-01.

The data collected for the study included a numerical identification code for the patient, which allowed their anonymization, patient sex, date of inclusion and exit from the cohort, year of birth and information on the prescription based on Anatomical, Therapeutic Chemical Classification System (ATC) codes. Table 1 presents all the active substances included in this study for which indications for use in patients aged less than 18 years have been approved in Spain.

To calculate the prevalence of antidepressant use in each year under study and its temporal trends, we counted the total number of prescriptions (were there more than 1) for different antidepressants given to each patient. The population on which we made these calculations comprised all individuals included in the BIFAP cohort in each year under study. Also, to analyse differences in prescribing based on patient sex, we analysed the total number of prescriptions made to male and female patients for each subgroup of antidepressants. Similarly, we analysed differences in prescribing based on patient age, excluding records for children under 6 years, as none of the active substances under study was indicated for use in this age group. We calculated the total number of prescriptions per subgroup of antidepressants by adding the prescriptions for all the active substances included in each of the subgroups.

Lastly, to assess whether antidepressant prescribing adhered to current recommendations, we divided records in 2 categories: prescription for indication of the active substance under conditions authorised by the AEMPS, and lack thereof.

Results

The number of prescriptions for antidepressants has been increasing, from 7.97 prescriptions per 1000 patients in 2013 to 8.87 prescriptions per 1000 patients in 2018, except in years 2014 and 2015 and between 2017 and 2018. The year with the greatest number of prescriptions in the period under study was 2016, and 2013 was the year with the fewest prescriptions. Table 2 shows the annual prevalence of antidepressant prescribing throughout the study period (2013–2018).

Analysing the trends in prescribing during the study period, we found an increase in the number of prescriptions per 1000 patients in the BIFAP in nearly all antidepressant subgroups. Selective serotonin reuptake inhibitors (SSRIs) remained the most frequently prescribed subgroup throughout the 6-year period, with a prescribing prevalence up to 5 points greater compared to the second leading subgroup, tricyclic antidepressants (TADs), peaking in 2016 (Fig. 1). The only exception involved norepinephrine reuptake inhibitors (NRIs), the least used subgroup, for which prescribing declined between 2013 and 2018. We observed a similar trend in norepinephrine and dopamine reuptake inhibitors (NDRIs), with prescriptions declining between 2013 and 2016, increasing to the initial frequency in 2017 and exceeding it in 2018.

On one hand, when it came to patient sex, we found that the temporal trends in the frequency of prescription were the same. We ought to highlight that the number of prescriptions per 1000 patients was greater in female patients compared to male patients in each of the years under study (Fig. 2). The temporal trends by antidepressant subgroup were the same in patients of either sex and were consistent with the overall trends.

On the other hand, we found that the number of prescriptions per 1000 patients in the BIFAP cohort increased progressively with age, and that this increase was more marked in adolescence (Fig. 3). This means that while in patients aged less than 13 years there were no differences based on sex (Fig. 4), the overall frequency of prescription (not taking age into account) was greater in female patients. We also found a decreasing trend in the frequency of prescription in patients aged 6–13 years throughout the study period.

Fig. 5 shows the variation in antidepressant prescribing in male and female patients based on whether the use of given active substances was indicated in the patient. Another difference between the sexes emerged, for while more prescriptions were made to female patients, the percentage of prescriptions that adhered to established indications was between 2% and 4% lower in female versus male patients throughout the study period.

The proportion of off-label antidepressant prescriptions increased with age, and therefore the proportion of indicated antidepressants decreased with age, with a predominance of off-label prescription in individuals aged 14 years or older (Fig. 6).

Discussion

Our findings evince a gradual increase in the frequency of prescription of antidepressants to children and adolescents in the period under study. This increase was consistent with what has been previously described by other authors in relation to the use of antidepressants and other psychotropic drugs. In recent decades, there has been a sustained increase in antidepressant prescribing in many countries, including countries in Western Europe and the United States. The prescribing prevalence rates found in the analysis of the BIFAP database were greater compared to the frequencies reported in Denmark, Germany, the Netherlands and France, but lower compared to the frequencies reported in the United States, Norway and the United Kingdom.[1,3,7,8,19–22] Revet et al.[7] found an increase of 3.9% in antidepressant prescribing between 2009 and 2016 in France, with the prevalence increasing from 0.51% to 0.53%. These values were very low compared to the results published by Hoffmann et al.,[8] who, analysing antidepressant prescription trends in Germany, Denmark, the Netherlands, the United

Table 1 Classification and indications of antidepressants authorised in Spain for use in individuals aged less than 18 years.

ATC code	Active ingredient	Indication
Tricyclic antidepressants (TAD)		
N06AA02	Imipramine	Nocturnal enuresis from age 5 years
N06AA04	Clomipramine	OCD and nocturnal enuresis from age 5 years.
N06AA06	Trimipramine	Depressive mood and anxiety and sleep disturbances from age 12 years.
N06AA09	Amitriptyline	Persistent nocturnal enuresis from age 6 years after failure of other approaches
N06AA10	Nortriptyline	Treatment de la depression, bipolar disorder and atypical depression from age 6 years.
N06AA12	Doxepin	Should not be used before age 18 years.
Selective serotonin reuptake inhibitors (SSRIs)		
N06AB03	Fluoxetine	Moderate to severe depression episodes in individuals aged more than 8 years who do not respond to psychotherapy.
N06AB04	Citalopram	Should not be used before age 18 years.
N06AB05	Paroxetine	Should not be used before age 18 years.
N06AB06	Sertraline	OCD from age 6 years.
N06AB08	Fluvoxamine	Should not be used before age 18 years.
N06AB10	Escitalopram	Should not be used before age 18 years.
Monoaminoxidase inhibitors (MAOIs)		
N06AF04	Tranylcypromine	Not recommended before age 18 years.
N06AG02	Moclobemide	Should not be used before age 18 years.
Dual serotonin and norepinephrine reuptake inhibitors (DSNRIs)		
N06AX16	Venlafaxine	Not recommended before age 18 years.
N06AX21	Duloxetine	Safety and efficacy not evaluated in paediatric age group
N06AX23	Desvenlafaxine	Safety and efficacy not evaluated in paediatric age group
Norepinephrine and dopamine reuptake inhibitors (NDRIs)		
N06AX12	Bupropion	Not recommended before age 18 years.
Selective norepinephrine reuptake inhibitors (NRIs)		
N06AX18	Reboxetine	Should not be used before age 18 years.
Atypical antidepressants		
N06AA21	Maprotiline	Not recommended before age 18 years.
N06AX03	Mianserin	Not recommended before age 18 years.
N06AX05	Trazodone	Not recommended before age 18 years.
Other antidepressants		
N06AX01	Oxitriptan	Should not be used before age 18 years.
N06AX11	Mirtazapine	Should not be used before age 18 years.
N06AX14	Tianeptine	Not recommended before age 18 years.
N06AX22	Agomelatine	Safety and efficacy not evaluated in paediatric age group
N06AX26	Vortioxetine	Not recommended before age 18 years.
Compounding		

Kingdom and the United States between 2005 and 2012 found increases ranging from 17.6% in the Netherlands to 60.5% in Denmark, where the prevalence increased from 0.61% to 0.98%. Of these 5 countries, Germany was the one with the lowest prevalence (0.48% in 2012). Hoffmann et al.[8] also observed an increase in Germany, where the prevalence rose from 0.32% in 2005 to 0.48% in 2012. Sarginson et al.[1] found similar results in the United Kingdom, where the prevalence of antidepressant prescription was 0.47% in 2002 and 0.49% in 2015. On the other hand, John et al.[21] explored this phe-

Table 2 Annual prevalence of antidepressant prescription per 1000 patients in the BIFAP cohort by patient sex and therapeutic subgroup.

Subgroup	2013				2014				2015			
	Female patients (n)		Male patients (n)		Female patients (n)		Male patients (n)		Female patients (n)		Male patients (n)	
	435 805		458 324		445 562		469 847		445 190		469 676	
	n	/1000	n	/1000	n	/1000	n	/1000	n	/1000	n	/1000
TADs	411	0.943	186	0.406	424	0.952	188	0.400	438	0.984	192	0.409
SSRIs	1483	3.403	1080	2356	1781	3997	1127	2399	1745	3920	1129	2404
Other	119	0.273	57	0.124	128	0.287	55	0.117	90	0.202	46	0.098
Atypical	30	0.069	16	0.035	43	0.097	23	0.049	44	0.099	27	0.057
DSNRIs	75	0.172	49	0.107	128	0.287	55	0.117	103	0.231	50	0.106
NRIs	8	0.018	17	0.037	8	0.018	15	0.032	6	0.013	14	0.030
NDRIs	5	0.011	6	0.013	8	0.018	15	0.032	11	0.025	6	0.013
MAOI	0	0.000	0	0.000	0	0.000	0	0.000	0	0.000	0	0.000
Total	2131	4.890	1411	3079	2520	5656	1478	3146	2437	5474	1464	3117
Annual rate	7968		8801		8591							

Subgroup	2016				2017				2018			
	Female patients (n)		Male patients (n)		Female patients (n)		Male patients (n)		Female patients (n)		Male patients (n)	
	436 326		460 773		427 566		451 185		433 312		457 013	
	n	/1000	n	/1000	n	/1000	n	/1000	n	/1000	n	/1000
TADs	424	0.972	179	0.388	421	0.985	194	0.430	435	1004	191	0.418
SSRIs	1800	4125	1185	2572	1765	4128	1123	2489	1720	3969	1124	2459
Other	117	0.268	48	0.104	116	0.271	58	0.129	137	0.316	71	0.155
Atypical	45	0.103	35	0.076	52	0.122	34	0.075	49	0.113	35	0.077
DSNRIs	93	0.213	43	0.093	88	0.206	38	0.084	97	0.224	42	0.092
NRIs	2	0.005	10	0.022	3	0.007	4	0.009	3	0.007	1	0.002
NDRIs	11	0.025	9	0.020	5	0.012	6	0.013	7	0.016	6	0.013
MAOIs	0	0.000	0	0.000	0	0.000	0	0.000	0	0.000	0	0.000
Total	2492	5711	1509	3275	2450	5730	1457	3229	2448	5650	1470	3217
Annual rate	8986		8959		8866							

DSNRIs, dual serotonin and norepinephrine reuptake inhibitors; MAOIs, monoaminoxidase inhibitors; NDRIs, norepinephrine and dopamine reuptake inhibitors; NRIs, selective norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TADs, tricyclic antidepressants.

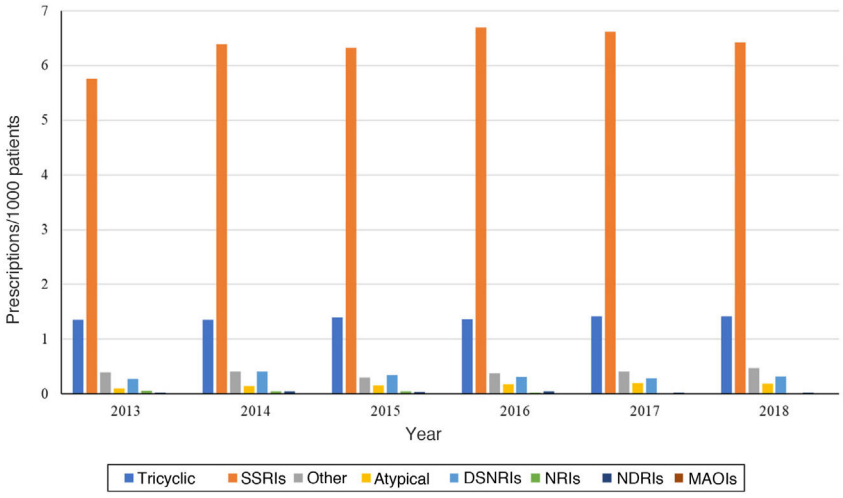

Figure 1 Annual prevalence of antidepressant prescribing per 1000 patients in the BIFAP cohort by therapeutic subgroup.

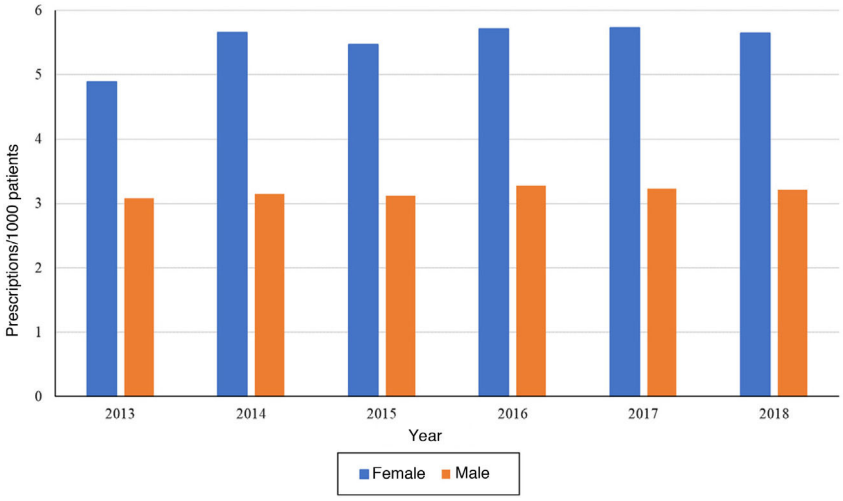

Figure 2 Annual prevalence of antidepressant prescribing per 1000 patients in the BIFAP cohort by sex.

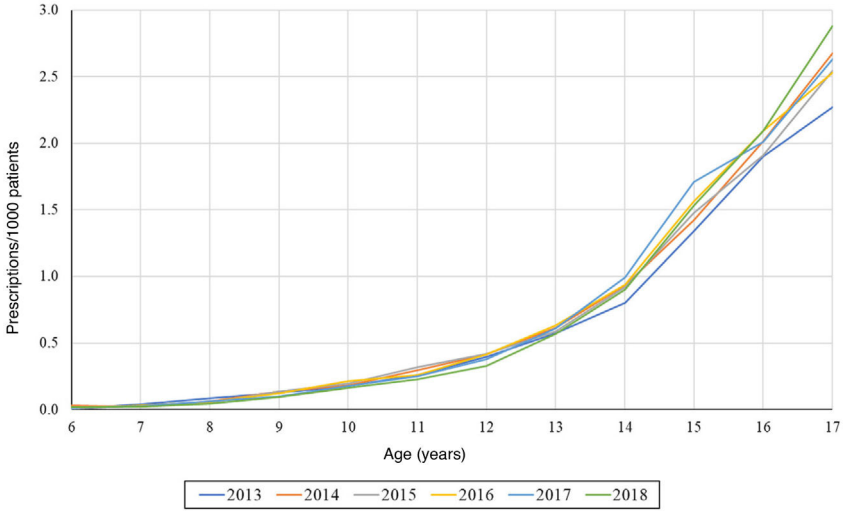

Figure 3 Annual prevalence of antidepressant prescribing per 1000 patients in the BIFAP cohort by age.

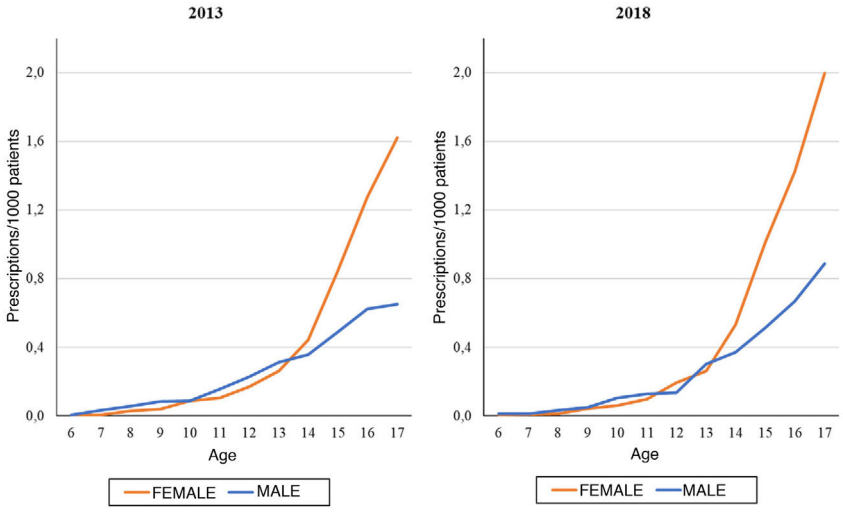

Figure 4 Annual prevalence of antidepressant prescribing by age and sex in years 2013 and 2018.

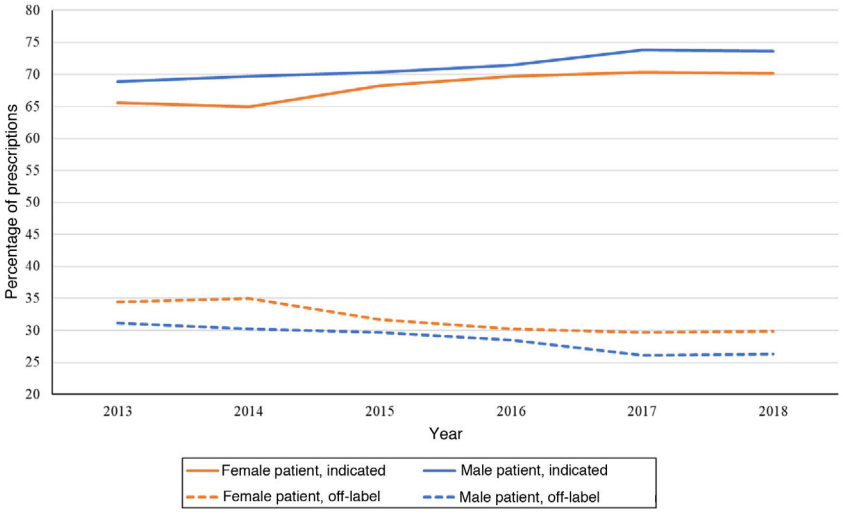

Figure 5 Proportion of prescriptions indicated and not indicated for individuals aged less than 8 years by sex.

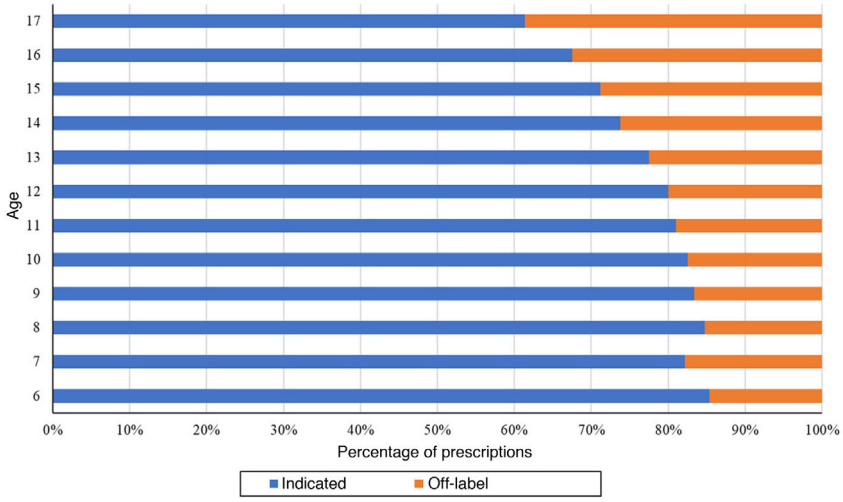

Figure 6 Proportion of prescriptions indicated and not indicated for individuals aged less than 18 years by age.

nomenon by analysing the incidence and not the prevalence, and found the same trend in the data, with an increase from 5.26 to 7.69 new prescriptions per 1000 individuals aged 6–18 years by year 2013.

Prescribing of the different antidepressant subgroups increased over the 6 years under study with the exception of NRIs and NDRIs. The decrease in reboxetine prescriptions could be due to the controversy surrounding its effectiveness compared to placebo, a lower response rate compared to SSRIs and higher rates of attrition compared to more recently developed drugs.[23,24] This was not the case in France, Germany or the United Kingdom, where prescription of TADs and other non-SSRI antidepressants has been steadily declining. When making this comparison, it is important to take into account that in Spain, 5 of the 7 antidepressants authorised for use in the paediatric population belong to the TAD subgroup. The predominance of SSRIs over all other types of antidepressants was a pattern consistent with the trends observed in other European countries and the United States. The most frequently prescribed active substance in patients in the BIFAP cohort was sertraline, followed by fluoxetine, in every year under study. This was consistent with the data published for countries like Sweden[2] or France,[7] while in Germany and the United Kingdom fluoxetine and citalopram were the most frequently prescribed antidepressants.[1,3,8,21]

The differences in prescribing observed between the sexes are not unique to this cohort, but have been described before repeatedly. We found a predominance of antidepressant prescribing in female minors, compared to the findings of Steinhausen et al.,[18] Hartz et al.[19] and Steffenak et al.[24] regarding treatment with other psychotropic drugs, such as stimulants. When considering the use of antidepressants in isolation, those authors also found the trend observed in our study.

Patient age is an important factor in this study, as most antidepressants should not be used in individuals aged less than 18 years (only 7 of the drugs in the analysis have indications for use in specific paediatric age groups specified in the summary of product characteristics). While the frequency of prescription increased with age, this was not a linear trend. The most significant increase took place in early adolescence, when trends change and prescribing becomes more frequent in female versus male individuals, which is consistent with the hypothesis that most mood and anxiety disorders have onset in this stage of development.[5,25] Between 2013 and 2018, the prevalence kept increasing overall, while decreasing in children aged 6–13 years, consistent with the findings of Revet et al.[7] in France, where there was a slight increase in the general population and in adolescents aged 12–17 years, but a decrease in children aged 6–11 years group. Similar results have been reported by Sarginson et al.[1] in the United Kingdom and Hoffmann et al.[8] in Germany. Other studies in several different countries have evinced increases in every age group.[2,19,26]

Despite the drawbacks of treatment with antidepressants in children and adolescents, both in regard to the authorization for their use by health care authorities and the risk-benefit ratio, especially considering aggressive behaviours and the risk of suicide,[27,28] our analysis evinced a large proportion of patients given prescriptions for active substances whose summaries of product characteristics do not include indications for these age groups. In 2013, such off-label prescriptions amounted to 33.12% of prescribed treatments, which stood in contrast to the data published by Lagerberg et al.[2]: in the same year, only 10% of antidepressant prescriptions in Sweden were for active substances not authorised for use in paediatric age ranges, once again with a higher proportion in adolescents. Although in the period under study off-label prescription gradually declined, 28.50% of the sample had off-label prescriptions in 2018. Revet et al.[7] also found a decline in the proportion of off-label prescriptions in the general population (6—17 years). Once again, there were differences based on sex, as the proportion of off-label prescription in male patients was 2%–4% lower compared to female patients in the overall sample, although these disparities between the sexes were nearly negligible at certain ages. We found a directly proportional association between age and off-label prescribing.

This study of the BIFAP cohort, as is the case of other studies conducted using databases, has a series of limitations. First of all, it is important to consider that most records correspond to prescriptions of an antidepressant, and data on their dispensation was rarely available. Thus, it is possible that the collected data do not reflect the actual use of these drugs, as we do not know whether they were eventually consumed. Secondly, we ought to highlight that an increase in the frequency of prescription is not necessarily due to an increase in the prevalence of one or more specific disorders, as the indications or diagnoses that motivated the prescription of the antidepressants were not documented. In addition, it is possible that the prevalence rates found in our study underestimate the actual prevalence in the total population, as the data only refer to prescriptions made by primary care physicians registered in the databases of 10 of the 17 autonomous communities in Spain. Therefore, it may not be possible to extrapolate the results to the entire population aged less than 18 years of Spain.

In conclusion, we can highlight that in the 6 years under study, we found evidence of an increased prevalence of prescribing to children and adolescents in the BIFAP cohort for most antidepressant subgroups. This increase was more marked in female individuals, in whom the prevalence of antidepressant prescription was greater compared to male individuals at all times. In younger children, the prevalence of prescription has been declining over time. In addition, it is much lower compared to the prevalence found in adolescents, and with a lower proportion of active substances used off-label. This does not justify the high percentage of treatments with drugs whose use is not authorised or is recommended against in the paediatric population. Given the adverse effects associated with antidepressant use and the

results of our study, we believe it would be advisable to carry out more studies regarding the risk-benefit ratio of these drugs in the paediatric age group and to seek safer treatment alternatives.

Conflict of interest

None.

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