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Mapping the scientific research on atypical antipsychotic drugs in Spain: a bibliometric assessment

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Objectives: We carried out a bibliometric study on the scientific publications in relation to atypical antipsychotic drugs (AADs) in Spain.

Methods: We used the *EMBASE* and *MEDLINE* databases and we applied some bibliometric indicators of paper production and dispersion (Price's law and Bradford's law, respectively). We also calculated the participation index of the different countries and correlated the bibliometric data with some social and health data (total *per capita* expenditure on health and gross domestic expenditure on research and development).

Results: We collected 656 original papers published between 1988 and 2011. Our study results fulfilled Price's law with scientific production on AADs showing exponential growth (correlation coefficient $r = 0.9693$, vs. $r = 0.9177$ after linear adjustment). The most widely studied drugs were risperidone (181 papers), olanzapine (143), clozapine (94), and quetiapine (74). Division into Bradford zones yielded a nucleus occupied by the *European Psychiatry* and *European Neuropsychopharmacology* (70 articles). Totally 194 different journals were published, with 5 of the first 10 used journals having an impact factor being greater than 4.

Conclusion: The publications on AADs in Spain have undergone exponential growth over the studied period, without evidence of reaching a saturation point.

Key words: Atypical antipsychotics, Bibliometry, Bipolar disorder, Schizophrenia, Spain

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La investigación sobre fármacos antipsicóticos atípicos en España: una evaluación bibliométrica

Objetivos: Se llevó a cabo un estudio bibliométrico de las publicaciones sobre fármacos antipsicóticos atípicos (AA) realizadas en España.

Método: Se usaron las bases de datos *EMBASE* y *MEDLINE* y se aplicaron indicadores bibliométricos de productividad y dispersión de artículos (leyes de Price y de Bradford, respectivamente). También se calculó el índice de participación (IP) de los diferentes países y se buscaron correlaciones entre los datos bibliométricos y algunos datos sociales y de salud (gasto total *per capita* en salud y gasto interior bruto en investigación y desarrollo).

Resultados: Se recopilaron 656 artículos originales publicados entre 1988 y 2011. Nuestros resultados constatan el cumplimiento de la ley de Price en la producción científica sobre AA, mostrando un crecimiento exponencial (coeficiente de correlación $r = 0,9693$ vs. $r = 0,9177$ después del ajuste lineal). Los fármacos más estudiados fueron la risperidona (181 artículos), la olanzapina (143), la clozapina (94) y la quetiapina (74). La división en zonas de Bradford dio lugar a un núcleo ocupado por las revistas *European Psychiatry* y *European Neuropsychopharmacology* (70 artículos). En total se publicaron artículos en 194 revistas diferentes, de las cuales 5 de las 10 primeras tenían un factor de impacto mayor de 4.

Conclusión: Las publicaciones sobre AA en España han experimentado un crecimiento exponencial en el período estudiado, sin evidencia de que se haya alcanzado un punto de saturación.

Palabras claves: Antipsicóticos atípicos, Bibliometría, Trastorno bipolar, Esquizofrenia, España

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INTRODUCTION

Schizophrenia is a severe mental illness with prevalence ranging in Spain between 0.2% and 0.7% of the population[1]. The main therapeutic pillar for schizophrenia during the last 60 years have been antipsychotic drugs. The so-called "psychopharmacological revolution" in the context of treating schizophrenic patients, began in the 1950s with the clinical introduction of chlorpromazine[2,3] and haloperidol[4]. These first drugs, called first-generation, classical or typical, biochemically characterized for blocking dopamine receptors, show a great efficacy at reducing schizophrenia positive symptoms (hallucinations, delusion, etc.). But their main limitation is side effects, principally extrapyramidal symptoms (EPS). After the reintroduction in the United States of clozapine, an antipsychotic drug commercialized in the 1960s, later withdrawn due to inducing agranulocytosis[5,6], the research expectations changed dramatically. Apart from causing few EPS, this agent showed efficacy in both positive and negative symptoms of schizophrenia as well as in patients who are refractory to other antipsychotic treatment[7]. Also, this drug had differential pharmacological characteristics,

especially at the level of the receptor blockage. Clozapine was the third cornerstone on the history of antipsychotic pharmacology, and opened the door to the so-called "atypical antipsychotics"[8] (AADs), with the introduction of risperidone in 1993.

As shown in Table 1, the advances achieved in the field of antipsychotic drugs in the past 20 years have been incredibly important, with the clinical introduction of numerous AADs (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, etc.). These agents have notably improved the quality of life of psychotic patients and have contributed decisively to weakening the stigmatization that has traditionally accompanied psychiatric attention[9]. With the clinical introduction of the new AADs since 1993 and, later on, with their licensing for treating bipolar disorder since 2003, consumption of these drugs has increased enormously. In Spain, AADs accounted for already 70% of prescriptions of antipsychotic drugs in 2006[10] and between this year and 2011 its use has increased by 51%. Clearly, the research on these drugs have also advanced considerably, and this has undoubtedly translated into a considerable increase in the amount of scientific

Table 1	Clinical development of atypical antipsychotic drugs		
	Company	**Launch**	
		International	**Spain**
Clozapine	Wander Laboratories	1972 [a] Switzerland	1993
Zotepine	Fujisawa	1982 [b] Japan	
Amisulpride	Synthelabo	1986 Portugal	2001
Risperidone	Johnson & Johnson	1993 UK / Canada	1994
Sertindole	Abbott Laboratories / Lundbeck	1996 [c] UK	1997
Olanzapine	Eli Lilly	1996 USA / UK	1996
Quetiapine	AstraZeneca	1997 USA / UK	2000
Ziprasidone	Pfizer	2001 USA	2002
Perospirone	Dainippon Sumitomo Pharma	2001 Japan	
Aripiprazole	Otsuka / Bristol-Myers Squibb	2002 USA	2004
Paliperidone	Janssen Pharmaceutica	2007 USA	2007
Blonanserin	Dainippon Sumitomo Pharma	2008 Japan	
Asenapine	Schering-Plough	2009 USA	2010
Iloperidone	Novartis AG	2009 USA	
Lurasidone	Dainippon Sumitomo Pharma	2011 USA	

[a] Reintroduced in 1990 in USA and UK after being withdrawn from the market in 1975

[b] Commercialized by Astellas in Germany in 1990

[c] Marketing authorization was suspended by the European Medicines Agency (EMA) in 1998 and the drug was withdrawn from the market. In 2002, based on new data, the EMA suggested that sertindole could be reintroduced for restricted use, and with extensive ECG monitoring requirement

literature on these drugs – as it has been analysed, in the specific case of Spain, in this study.

Investments in health care to mentally ill patients in Spain are similar to those of other European countries. Total health expenditure in Spain accounted for 9.5% of gross domestic product (GDP) in 2009[11]. Although the actual percentage expended in mental care is not known and estimates are unreliable, about 5% of total health expenditure can be attributed to mental health[12]. However, the rate of psychiatrists per 100,000 population is lower (8 vs. 15 in the mean value of the first 27 countries of the Organisation for Economic Co-operation and Development[13]). To improve some parameters, the Spanish Ministry of Health published in 2006 the document Mental Health Strategy in National Health System, one of which 6 strategic lines is the research in mental health (including psychopharmacological research)[14]. In any case, Spanish psychiatric research was already represented in publications of greater impact factor of the speciality and was comparable in volume to the other countries of our surroundings[15,16].

The use of bibliometric indicators for studying research activity in a specific country in a particular field is based on the premise that scientific publication is the essential result of such activity[17]. Bibliometric studies are useful tools for assessing the social and scientific relevance of a given discipline or field[18]. Our group has studied, with a bibliometric approach, the evolution of scientific literature in psychiatry by specific research groups, on different psychiatric disorders, on aspects related to the discipline, and on specific therapeutic tools in the field of psychopharmacology[15,19-25]. Here, we specifically carried out this bibliometric study on AAD publications in Spain.

METHODS

The databases used in this bibliometric study were MEDLINE (Index Medicus, U.S. National Library of Medicine, Bethesda, Maryland, USA) and Excerpta Medica (Elsevier Science Publishers, Amsterdam, Netherlands), which are considered the most exhaustive databases in the biomedical field, and which both participate in EMBASE Biomedical Answer web (Elsevier B.V.).

With remote downloading techniques, we chose papers containing, in the AD (author address) section the descriptor Spain, and in the TI (title) section, the descriptors atypic* (atypical*) antipsychotic*, second-generation antipsychotic*, clozapine, risperidone, olanzapine, ziprasidone, quetiapine, sertindole, aripiprazole, paliperidone, amisulpride, zotepine, asenapine, iloperidone, lurasidone, perospirone and blonanserin, published in the period from 1988 to 2011. The

rest of the descriptors, referring to pharmacological aspects, were not restricted to any field of the database. For the purposes of this study we considered all original articles, brief articles, reviews, editorials, letters-to-the editor, etc., and all duplicated papers were omitted. In this regard, the database used permits the elimination of items that may be duplicated in each of the databases (MEDLINE and EMBASE).

With manual coding after studying the title and/or abstracts of the articles, we divided those papers into four groups: "experimental pharmacology," "clinical efficacy," "tolerance and/or safety," and "not specified group."

Among the bibliometric indicators of production we applied Price's law[26]. This law is the indicator most widely used in analysing the productivity of a specific discipline or a particular country, to reflect a fundamental aspect of scientific production, which is its exponential growth. To assess whether the growth of scientific production in AADs follows Price's law of exponential growth, we made a linear adjustment of the data obtained, according to the equation $y = 3.6422x - 18.152$, and another adjustment to an exponential curve, according to the equation $y = 1.071e^{0.1997x}$.

As a bibliometric indicator of the dispersion of scientific information, we used Bradford's law. With the aim of revealing the distribution of the scientific literature in a particular discipline, Bradford proposed a model of concentric zones of productivity (Bradford zones) with decreasing density of information[27]. Thus, each zone would contain a similar number of papers, but the number of journals in which these are published would increase on passing from one zone to another. This model permits identification of the journals most widely used or with greatest weight in a given field of scientific production.

We used the impact factor (IF) as an indicator of the publications' repercussion [28]. This indicator, developed by the Institute for Scientific Information (Philadelphia, Pennsylvania, USA), is published annually in the Journal Citation Reports (JCR) section of the Science Citation Index (SCI). The IF of a journal is calculated on the basis of the number of times this journals is cited in the source journals of the SCI during the two previous years and the total number of articles published by the journal in question in these two years. The JCR lists scientific journals by specific areas, ascribing to each of them their corresponding IF and establishing a ranking of "prestige"[28]. We used the IF data of 2011 published in the JCR of 2012.

Another indicator included in the present analysis is the national participation index (PI) of Spain for overall scientific production (the ratio of the number of papers generated by Spain and the total number of papers on this

topic). This PI has also been compared with global PI in biomedical and health sciences (as well as for Psychiatry and Neurology area in particular). Likewise, the PI has been correlated with some health data, such as total *per capita* expenditure on health and gross domestic expenditure on research and development (R&D). The PI has also been correlated with the corresponding PI for the world's 15 most productive countries during the period from 1988 to 2011. Its health data were obtained from the OECD Health Division[11], and WHO Department of Health Statistics and Informatics[29].

RESULTS

After study of the analysed database, during the period from 1988 to 2011, we obtained 656 original papers (articles, reviews, editorials, letters-to-the-editor, etc.) dealing with different aspects related to AADs in Spain. Of

these, 181 papers correspond to risperidone, 143 to olanzapine, 94 to clozapine, 74 to quetiapine, 41 to aripiprazole, 37 to ziprasidone, 29 to paliperidone, 21 to amisulpride, 2 to sertindole, and 1 to asenapine, blonanserin, iloperidone and lurasidone, each. We did not find any paper on zotepine and perospirone. Zotepine, perospirone, blonanserin, iloperidone and lurasidone are not available in Spain.

As illustrated in Figure 1, over the last 25 years there has been a marked increase in the number of AAD publications generated in Spain. As shown in Figure 1, the mathematical adjustment to an exponential curve permitted us to obtain a correlation coefficient $r = 0.9693$, indicating 6.05% of variance unexplained by this fitting. In contrast, the linear adjustment of the measured values provides an $r = 0.9177$, and therefore a percentage of unexplained variance of 15.78%. With these data, we can conclude that the database analysed was more in keeping
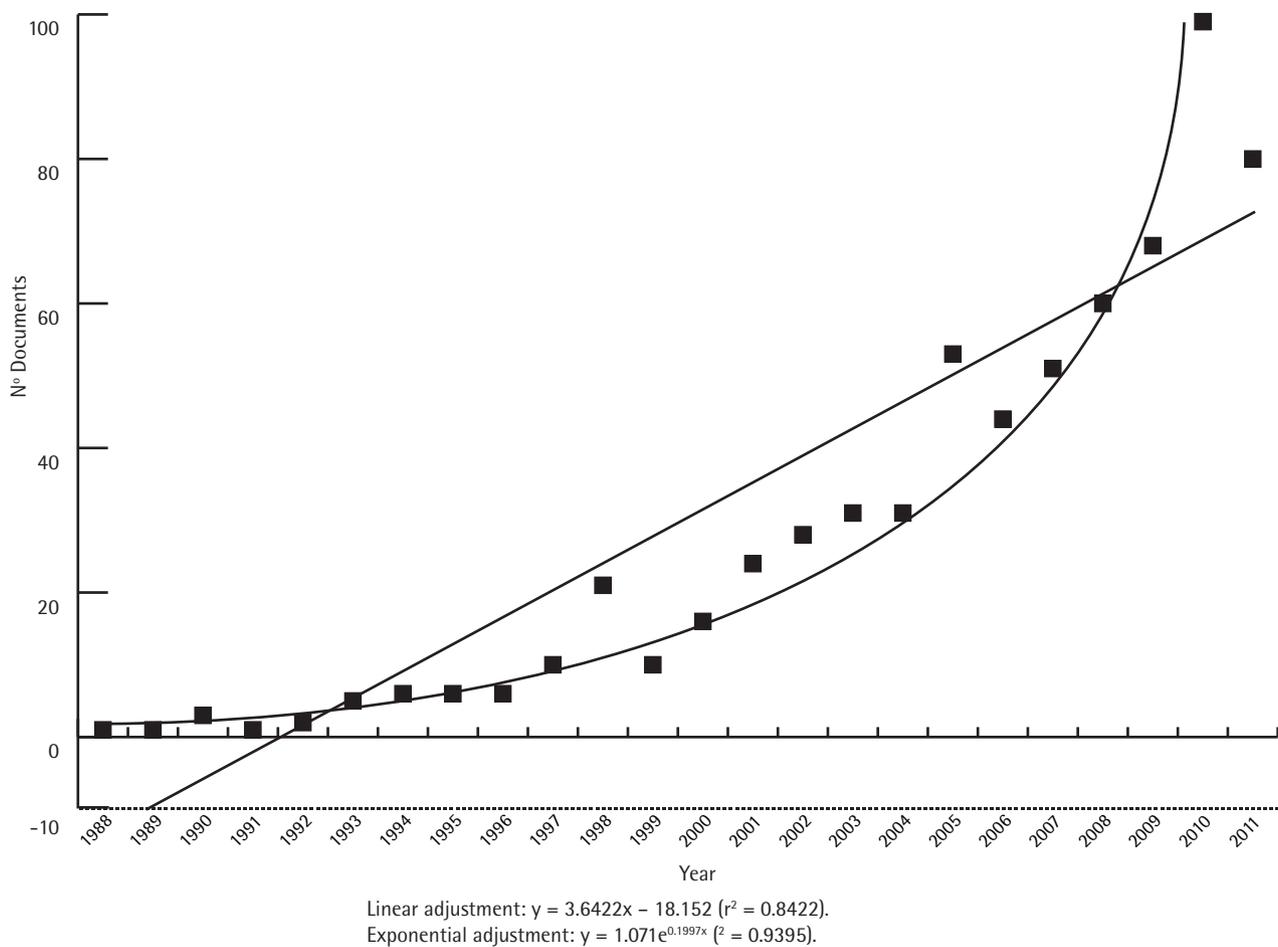

Linear adjustment: y = 3.6422x – 18.152 (r² = 0.8422).
Exponential adjustment: y = 1.071e$^{0.1997x}$ (² = 0.9395).

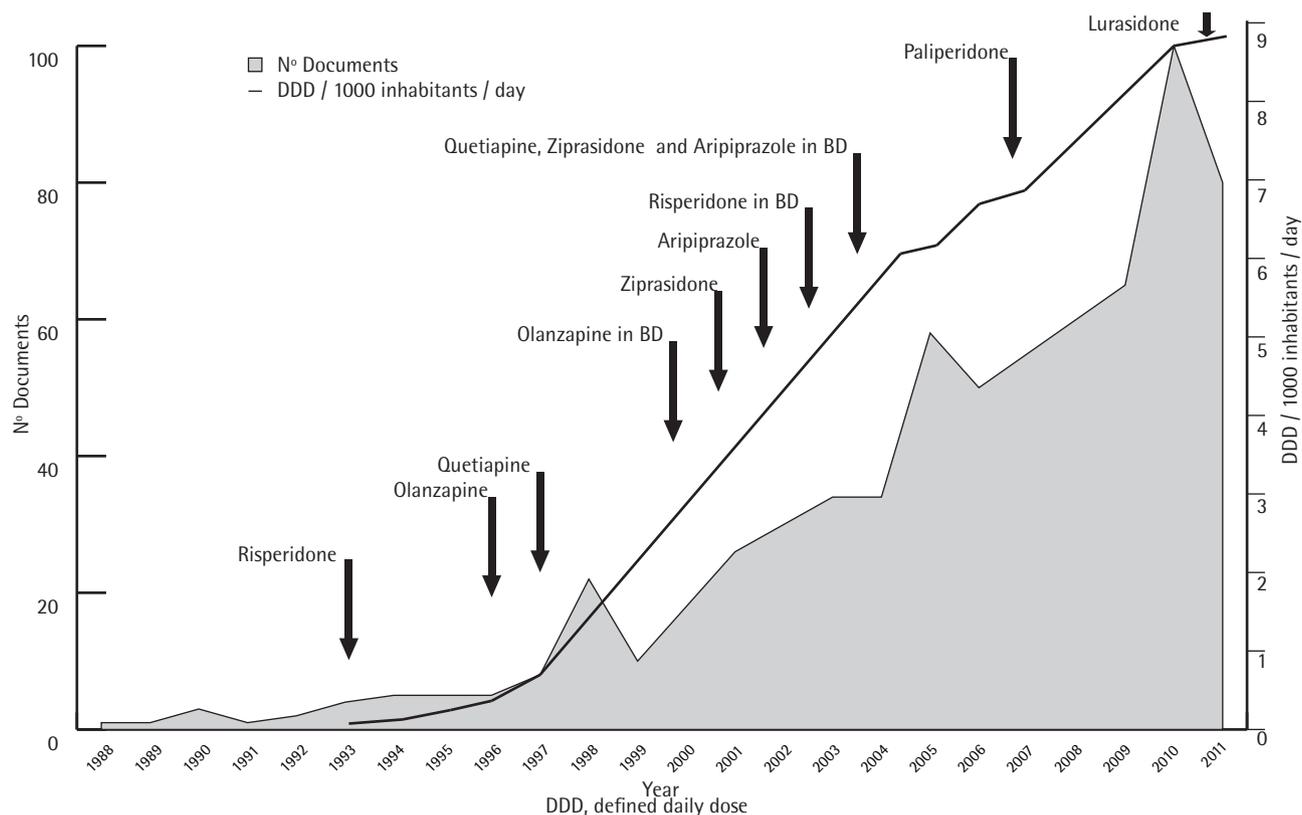| Figure 1 | Growth of scientific production on atypical antipsychotic drugs in Spain. A linear adjustment of the data was carried out, and a fitting to an exponential curve for AAD papers according to Price's law[26] was found |

Figure 2 | Number of documents on atypical antipsychotic drugs (1988-2011), use of atypical antipsychotic drugs in Spain, and international licensing of different drugs

with an exponential fitting than a linear one, and that the postulates of Price's law were fulfilled.

The clinical introduction of the new AADs in different countries of the world, together with their licensing for treating bipolar disorder, is to have contributed substantially to the increase in scientific production in the AADs field in Spain, as can be seen in Figure 2. This growth is closely correlated with the consumption data of AADs in Spain. Further, Figure 3 depicts the evolution that has occurred in the last two decades of all AAD papers. With effects from 2004 and 2008, the growth was mainly due to risperidone, and aripiprazole and quetiapine, respectively. Figure 4 illustrates the matter even better, by showing that cumulative growth in total AAD scientific production in Spain was increased in each five-year period compared to the previous one with even gradual increment. This growth was always higher (in the four consecutive five-year periods) compared to the global growth of Spanish science in biomedicine and health, and to the specific field of Psychiatry and Neurology.

As regards to the scientific journals in which the AAD papers had been published, we applied the Bradford's model. The mean number of articles per Bradford zone was 65.60, though if we discarded the last zone, whose accuracy was obviously lower, the mean would be 72.88. Table 2 shows the division into Bradford's areas of the papers in this study. The nucleus or first zone would be made up of the *European Psychiatry* and *European Neuropsychopharmacology*, with 36 and 34 papers, respectively, and the second zone *Journal of Clinical Psychopharmacology* (*n* = 27), *Actas Españolas de Psiquiatría* (*n* =27) and *Journal of Clinical Psychiatry* (*n* = 22). The rest of the journals analysed are included in zones 3 to 10. A total of 194 different journals were used to publish those papers analysed. To note, the 10 most used journals accounted for 34.29% of all papers in this study.

Table 3 shows these 10 journals most used for the diffusion of scientific AAD papers by Spanish authors and their corresponding IFs, according to the *JCR* of 2011, and the PI of the journals on total database in the analysed period. The journals (Table 3) most extensively used for the diffusion of AAD papers have high IFs (7 and 5 of them having an IF being greater than 2 and 4, respectively).

Manually classifying articles, we found that 52.54% of them belonged to the "clinical efficacy" group, 18.65% to the "tolerance and safety" group, 18.79% to the

Table 2	Distribution of the journals in Bradford's zones		
Zones	Number of journals	Number of articles	Bradford's constants
	2	70	
2	3	76	1.5
3	4	67	1.33
4	7	75	1.75
5	8	67	1.14
6	14	72	1.75
7	24	70	1.71
8	43	70	1.79
9	70	70	1.62
10	19	19	

Total number of journals = 194
Average number of articles = 65.60
Average number of articles, excluding the last Bradford zone = 72.88

Table 3	The 11 journals with highest number of publications on atypical antipsychotic drugs from Spain		
Journal	Nº Documents	PI	IF [a]
European Psychiatry	36	5.49	2.766
European Neuropsychopharmacology	34	5.18	4.046
Journal of Clinical Psychopharmacology	27	4.11	4.098
Actas Españolas de Psiquiatría	27	4.11	0.589
Journal of Clinical Psychiatry	22	3.35	5.799
Progress in Neuro-Psychopharmacology and Biological Psychiatry	21	3.20	3.247
Schizophrenia Research	19	2.89	4.748
Medicina Clínica	14	2.13	1.385
International Journal of Neuropsychopharmacology	13	1.98	4.578
Psiquiatría Biológica	12	1.82	-
Anales de Psiquiatría	12	1.82	-

PI, participation index; IF, impact factor 2011
[a] *Journal Citation Report*, 2011 (JCR, 2012)

"experimental pharmacology" group, and 10.02% to the "not specified" group (mainly, general reviews, pharmaco-economic analysis and articles of prescribing patterns). Clinical studies are mainly devoted to schizophrenia (n = 139) and bipolar disorder (n = 85), and to a lesser extent, to substance abuse disorders (n = 12), depressive disorders (n = 8) and Parkinson disease (n = 8).

The general contribution of Spanish science, within this thematic area, represents a global PI of 3.59 (sixth in the ranking) with respect to world production in period
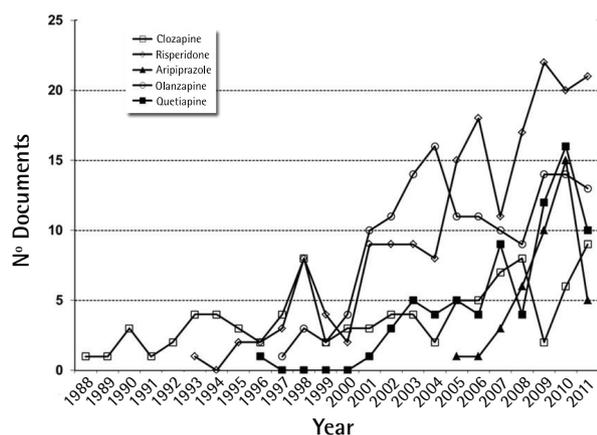

Figure 3	Evolution of scientific papers on five most relevant atypical antipsychotic drugs (based on MEDLINE and EMBASE from 1988 to 2011)

analyzed. Table 4 shows that among the countries generating most significant AAD research, the USA (whose PI is 32.12), is most significant, followed by the United Kingdom (PI = 6.73), Germany (PI = 6.32), Canada (PI = 4.93) and Italy (PI = 4.59).

If we consider the paper productivity of these countries in the field of Psychiatry and Neurology, only 4 (Spain, India, Sweden, and Brazil) of the 15 largest producers in biomedicine and health sciences (in the period of 1988-2011) devoted a higher percentage of attention to the AAD study (Figure 5). Figure 6 shows the correlation between PI and the *per capita* health expenditure and the gross domestic expenditure on R&D of each of the countries with the highest scientific production in health sciences.

Table 5 shows the most Spanish productive institutions to produce AAD papers in this study. As it can be seen, only 26.67% of total production was generated in the top ten institutions. But the rakings here are solely based on the information given in the AD field in the *EMBASE* Biomedical Answer web database, *i.e.*, we identified affiliated institutions of the author address of those AAD papers in this study.

Table 4	Distribution of documents on atypical antipsychotic drugs in the world's 15 most productive countries in biomedicine and health sciences for the period of 1988-2011				
	Country [a]	% [a]	Psy-Neurol [b] (%)	AADs (%)	AA/Psy-Neurol
1	USA	25.45	35.78	32.12	0.91
2	UK	7.15	9.55	6.73	0.69
3	Japan	6.57	6.89	3.63	0.53
4	Germany	6.05	7.71	6.32	0.83
5	France	4.48	4.99	3.39	0.69
6	Italy	3.77	4.73	4.59	0.98
7	Canada	3.55	4.95	4.93	1.01
8	China	3.46	2.63	2.04	0.79
9	Spain	2.49	2.76	3.59	1.32
10	Australia	2.31	2.93	2.41	0.83
11	Netherlands	2.28	2.86	2.36	0.84
12	India	1.72	1.29	2.33	1.82
13	Sweden	1.56	1.88	2.01	1.08
14	Switzerland	1.48	1.77	1.10	0.68
15	Brazil	1.18	1.22	1.26	1.04

Psy-Neurol, area of focus in Neurology and Psychiatry; AADs, atypical antipsychotic drugs
[a]The world's 15 most productive countries in biomedicine and health sciences for the period of 1988-2011, and [b] Their productivity in the discipline of Psychiatry and Neurology
Total documents 1988-2011: 16,207,619
Total documents in Neurology & Psychiatry Area 1988-2011: 1,808,248

Table 5	Contribution of atypical antipsychotic drug papers from different institutions in Spain	
Institution		n
Hospital Clinic de Barcelona		48
Hospital General Universitario Gregorio Marañón (Madrid)		20
Institut d'Investigacions Biomediques August Pi i Sunyer - IDIBAPS (Barcelona)		16
Hospital Clínico de Salamanca		15
Universidad de Santiago de Compostela		15
Hospital de la Santa Creu y Sant Pau (Barcelona)		14
Lilly Research Laboratories (Alcobendas, Madrid)		11
Laboratorios Esteve, S.A. (Barcelona)		10
Hospital Universitario Marqués de Valdecilla (Santander)		9
Universidad de Extremadura (Badajoz)		9
Hospital Psiquiátrico Dr. R. Lafora (Madrid)		8

n, number of documents in the study database

DISCUSSION

As shown in Figure 1, we found that in this study the number of scientific publications had exponentially grown over the last 25 years, especially after 2004, and that the growth up to the end of this study did not reach saturation postulated by Price in his theory of expansion of scientific literature[26]. As indicated in Figure 2[10], these bibliometric data were closely related to the prescription data, which have been increased significantly in Spain during the last decade[30-31]. In fact, DDD (defined daily dose / 1,000 inhabitants / day) of AADs in Spain exceeded the classical antipsychotic drugs in 2001, and units sold in 2010 [10].

The increased published AAD papers on were found to be coincidental with the approval for marketing by the US Food and Drug Administration (FDA) and other international regulatory agencies in treating bipolar disorder. Since 2004, other AADs such as risperidone, quetiapine, ziprasidone, aripiprazole, and asenapine, etc. have been also approved for treating manic episodes, and olanzapine and aripiprazole for relapse prevention in patients with bipolar disorder[32]. Quetiapine is indicated as monotherapy for the acute and maintenance treatment of depressive episodes of bipolar disorder, and as an add-on treatment
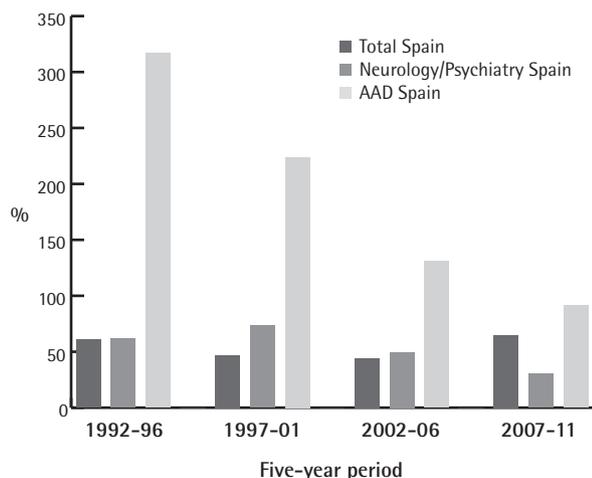
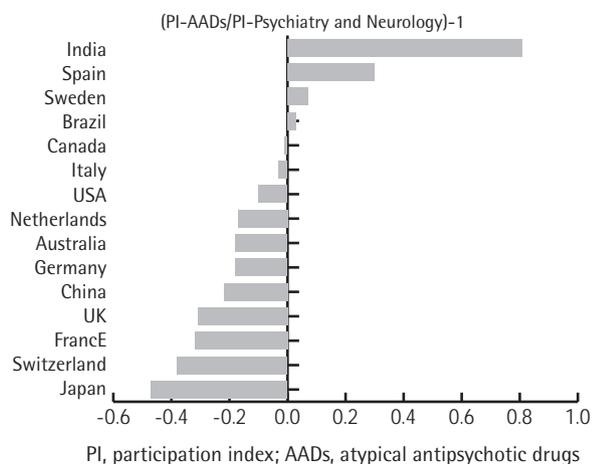| Figure 4 | Cumulative growth by five-year periods of scientific production on total productivity in biomedicine and health sciences, Psychiatry and Neurology area, and atypical antipsychotic drugs in Spain. Data from each five-year period refer to evolution over the previous period. The period of reference is 1987-91 |

| Figure 5 | Relationship between production of scientific literature on atypical antipsychotic drugs and total production in the field of Psychiatry and Neurology in the world's 15 most productive countries in biomedicine and health sciences |

of major depressive disorder when antidepressants alone have not been sufficiently effective. Olanzapine-fluoxetine combination is indicated for treating treatment-resistant major depressive disorder. Aripiprazole was also approved

in 2007 by the FDA as an add-on to the existing antidepressant for treating treatment-resistant major depressive disorder[32]. As indicated in Figure 3, an obvious upsurge in the five-year period of 2002-06 was found, coinciding with the period of official approval of the new AADs and their new indications (bipolar disorder, depression, autism, etc.). In the individual analysis of the new AADs, risperidone was found to be the agent most widely studied in Spain.

AADs are also commonly used (and studied) in many off-label indications, such as substance-induced psychosis, agitation symptoms, tics, substance abuse disorders, etc.[31,33-34]. The Spanish Association of Dual Diagnosis (Sociedad Española de Patología Dual) was founded six years ago by psychiatrists who had worked in the drug network and are now integrated into the mental health network. These association members have learned to prescribe AADs safely and comfortably, with their AAD being favorably used in treating substance abuse disorders. Those afore-mentioned two factors might have caused the increased of publications on AAD in Spain.

To analyse the quality of papers from Spain, we used the indicators of impact and excellence of the publications on the topic in question. The fact that prestigious journals such as *Journal of Clinical Psychiatry* (IF = 5.799), *Schizophrenia Research* (IF = 4.748), or *International Journal of Neuropsychopharmacology* (IF = 4.578) published articles on AADs from Spain is an important factor, indicating the relevance (both clinical and social) that this country has acquired in recent years. To note, among the 10 publications most widely used in Spain for the international divulgation on AAD research, five journals are in the ranking of the most relevant in the field of Psychiatry (IF in 2011 being greater than 4).

Psychiatric research in Spain went through a remarkable increase in quality and quantity of peer-reviewed papers during the last two decades, being in parallel with other biomedical disciplines[15-16,35]. Comparing the periods of 1994-1995 and 2001-2002, we found that the Spanish research production was doubled[8]. Although during the decade of 1980-1989 only 3% (approximately) of all scientific publications on Spain were mental health, our results showed that during the period of 1988-2011, the percentage of papers in the area of Psychiatry and Neurology accounted for 12.36% of the total scientific production in Spain. As we have shown in recent studies[24-25], scientific AAD research is one of the fastest growing fields within the field of psychiatry. Similarly, some authors with bibliometric tools, have reported the research activity in the field of schizophrenia being superior to that of other fields of psychiatry[36]. These authors also suggest that the attraction of research on schizophrenia may have been
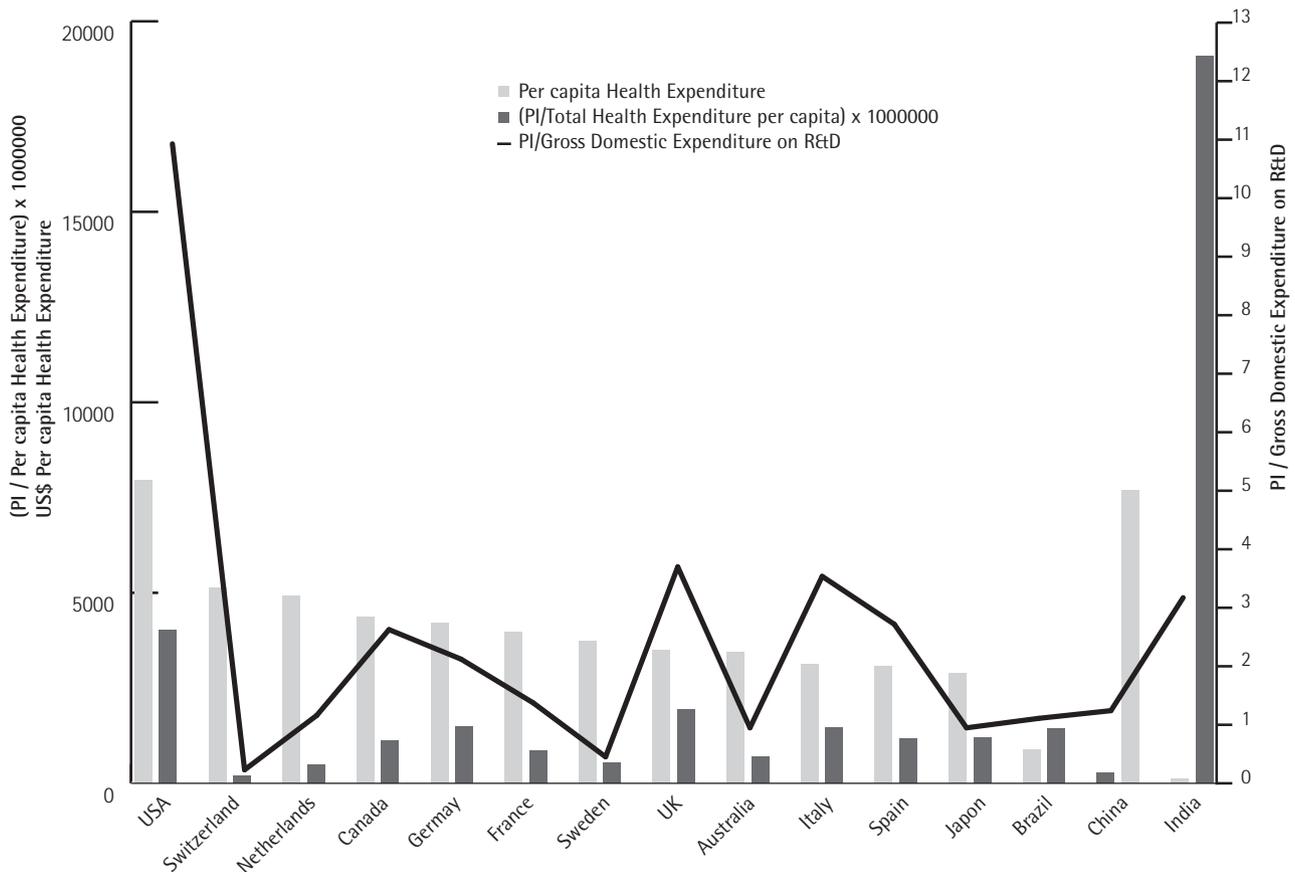
AADs, atypical antipsychotic drugs; R&D, research and development; PI, participation index; PPP, purchasing power parity
Total health expenditure per capita PPP US $ (data from the Organization for Economic and Co-operative Development [OECD] 2009)[11]
Japan and Australia; Data 2008
China, India and Brazil: Total health expenditure per capita PPP Int $ (data 2008)[29]
Gross domestic expenditure on R&D (%). Data OECD 2010, except USA and Japan (data 2009), Australia and Switzerland (data 2008), China (data 2007), Brazil (data 2006) and India (data 2004)

| Figure 6 | Per capita health expenditure and relationship between production of scientific literature on atypical antipsychotic drugs and per capita health expenditure and gross domestic expenditure on R&D, in the world's 15 most productive countries in biomedicine and health sciences |

positively affected by the clinical perception of the greater seriousness of the illness compared to other psychiatric pathologies. Moreover, Theander and Wetterberg report that the number of references on schizophrenia in *MEDLINE* has followed the general increase of medical publications, which accounts for 0.42% compared to the total medical literature in the studied period[37].

The two major English-speaking countries, USA and UK, head the ranking of paper-producing countries, generating totally over a third of total scientific production in this field (38.85%). Both countries are home to the pharmaceutical companies responsible for the development of AADs (olanzapine – Eli Lilly, USA; risperidone and paliperidone – Janssen Pharmaceutica, USA; quetiapine –

AstraZeneca, UK; ziprasidone – Pfizer, USA; and aripiprazole – Bristol-Myers Squibb/Otsuka Pharmaceutical Co., USA/Japan). This fact may help explain why both USA and UK have high PI.

Table 4 shows the data from the 15 most productive countries in biomedicine and health sciences and compares the data for general productivity in the Psychiatry and Neurology discipline with productivity in the specific AAD field. To note, Spain, Sweden, India and Brazil sit near the top of the ranking for AAD production (see also Figure 5), reflecting the special interest of these countries in research into these drugs. But Italy and Canada, maintain rates of productivity in AAD research that are–proportional with their global index for psychiatry. Contrariwise, Japan,

Switzerland, France, or UK has lower relative interest in these drugs, within the context of their general production in psychiatry.

Figure 6 shows the correlation of scientific production in AADs with the *per capita* health expenditure of each country, offering a similar view of this phenomenon, confirming the notion that the higher the spending on health, the greater the research production. A country's scientific production in a given field tends to reflect that science research and development policy began some years before the period analysed, and that they are not the fruit of particular economic circumstances[21-23]. In Spain, during the last decade, all new hospitals built (both big general hospitals and small regional hospitals) have provided brief hospitalization units with residents in psychiatry, which has culminated a process of constant medicalisation of psychiatry. This has contributed to being able to carry out many AAD studies. It is striking, however, to observe the low ratios of countries such as Australia, France, Sweden, Switzerland or Netherlands. On the contrary, we consider that the data for China and India are artifacts due to the small *per capita* health expenditure of these countries (265 purchasing power parity (PPP) Int $ for China and 122 PPP Int $ for India)[29].

The correlation analysis between scientific AAD production and the gross domestic expenditure on R&D located to Sweden and Switzerland in the last two positions. Spain ranks third in the ranking, behind UK and Italy. In this sense, the greatest number of research projects obtaining funding from the "Fondo de Investigación Sanitaria," a main public funder in Spain, have been in the thematic area of Neurological and Mental Diseases (15.52%)[38]. Totally 44 projects were funded in 2001 (€ 2.08 million), 337 in 2005 (€ 12.25 million), and 118 in 2010 (€ 12.02 million)[14,38]. Moreover, the research at the Carlos III Research Institute were predominantly biologically driven in strategies. As part of this institution were created in 2006 Networks and Cibers, such as CIBERSAM, which groups most of the research teams of Spain, where schizophrenia and bipolar disorder take up most of the resources, both public and private. Within these disorders, AADs have played a leading role. This correlates closely with results obtained in this study.

LIMITATIONS AND STRENGTHS OF THE STUDY

The readers are warned against over-interpreting the study findings because this study has three major limitations which are inherent to its bibliometric nature[39]. First, not all the AAD papers from Spain were included. This bibliometric study includes papers from *EMBASE* Biomedical Answer web. The criteria set by the databases themselves determine the subsequent development of the studied

materials[17,40]. Excluded are those papers on AADs if authors do not put the AAD descriptors in the titles or key words of the papers, national or local journals that are not included in *MEDLINE* and *Excerpta Medica*, and those contributions at scientific conferences and meetings[19]. Second, we included only those papers with Spanish corresponding authors in this study. And third, the use of indicator impact factor to determine the merit or quality of scientific contributions is still debatable. The citation count may mean that the given topic is the study is "not yet mature" and is "in need of more studies." But it may not mean the work is more important than those papers which do not get many citations. Differing in those in the Europe and Asia, American universities do not use impact factor as much to measure the production of a faculty member.

In spite of the above-listed study limitations, bibliometric studies are useful in assessing the social and scientific relevance of a given discipline or field[18]. Those studies constitute an effective complement for the opinions and judgments of experts in each field, giving useful and objective tools to evaluate the results of scientific activity, offering a more realistic view of the picture and an indication of trends, as well as predicting how it might evolve[41].

CONCLUSION

Keeping in mind of the above-listed limitations and strengths, we have been able to offer a picture of the representativeness and evolution of international research on AADs in Spain, observing the parameters of quality and dissemination most commonly employed at an international level. This study results confirm that the research in AADs carried out in Spain have a good level currently and has made a positive evolution in the last two decades, similar to what happened in other fields of biomedical research[16].

AADs as a group of pharmaceutic class started to become number 1 in the market sale (US$ 14.6 billion per year) in 2008 in the USA[32]. Any new AAD, as a commercial commodity, can easily become an instant "mega-drug" (by the definition of having the annual sale of US$ 500 million) if it can occupy only 4% of market share in the USA[32]. Thus, research in this field will definitely continue to grow in the coming years. To note, the ideal antipsychotic drug has not yet been found[9], and that the need of treating many treatment-resistant patients is waiting to be met[41].

Besides, AADs have, and will continue to have, an ever-expanding range of clinical indications, both within the psychiatric ambit and outside it, to judge from the promising results obtained for the different pathologies

with which they have been studied[34]; in consequence, scientific production in relation to these drugs will certainly continue to be abundant.

CONFLICT OF INTEREST STATEMENT

The authors do not have any conflict of interest, including financial support.

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