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Research report

Bipolar disorder as an emerging pathology in the scientific literature: A bibliometric approach

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Abstract

Background: To carry out a bibliometric study on the scientific publications in relation to bipolar disorder.
Methods: Using the EMBASE and MEDLINE databases, we selected those documents whose title included the descriptors *bipolar disorder**, *bipolar illness*, *bipolar patient**, *bipolar mani**, *bipolar depress**, *bipolar spectrum*, *manic–depressive**, and *rapid cycling*. We applied some bibliometric indicators, as Price's Law on the increase of scientific literature, or the participation index (PI) of the different countries. The bibliometric data have also been correlated with some social and health data from the countries that are most prolific in biomedical scientific production, such as number of physicians, total per capita expenditure on health and overall volume of production in the field of psychiatry.
Results: A total of 4270 original documents published between 1980 and 2004 were downloaded, of which 1825 corresponded to aspects related to drug therapy. Our results state fulfilment of Price's Law, with scientific production on bipolar disorder showing exponential growth (correlation coefficient $r=0.947$, as against an $r=0.849$ after linear adjustment). The drugs most widely studied are lithium (1351 documents), valproate (544), carbamazepine (493), lamotrigine (240), and olanzapine (210). United States is the most productive country (participation index, PI=44.2), followed by the United Kingdom (14.4), Netherlands (9.1) and France (4.1).
Conclusion: The publications on bipolar disorder and mood stabilizers have undergone exponential growth over the last 25 years, without evidence a saturation point.

Keywords: Bipolar disorder; Bibliometry; Mood stabilizers; Antipsychotics; Anticonvulsants

1. Introduction

Bipolar disorder is one of the psychiatric conditions that has received most attention in the scientific literature in recent years. It is a serious mood disorder, of a chronic nature, characterized by continual or irregular alternate episodes of mania/hypomania with euthymia/depressive episodes (Vieta, 2005). Bipolar disorder, known

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classically as manic–depressive illness or psychosis, presents significant morbi-mortality (Bauer and Pfenning, 2005), with a prevalence over the lifespan of between 1% and 2% of the population over the age of 20 (Goodwin and Jamison, 1990). Nevertheless, there is currently a tendency to consider the pathology as a whole from a broader perspective, taking into account all the cases with less apparent and obvious clinical features. This form of understanding the illness, in terms of a "bipolar spectrum", would imply prevalence rates of between 2.8% and 6.5% of the population (Bauer and Pfenning, 2005; De Lima et al., 2005).

Improved knowledge of the clinical and diagnostic aspects of bipolar disorder appears to have been accompanied by improvements in therapeutic aspects. The discovery of the antimanic properties of lithium salts in 1949, by the Australian psychiatrist John Cade, opened the door for bipolar disorder to pharmacological therapy (Cade, 1949). Today, in spite of its limitations, lithium retains a privileged place within the arsenal of therapeutic drugs, being considered by many clinicians and researchers as the "gold standard" of mood stabilizers. The subsequent incorporation of carbamazepine and valproate as mood regulator agents began a trend that appears to have flourished in the last decade (Pope et al., 1991). In recent years, the new anticonvulsant drugs, which have revolutionized the treatment of epilepsy, have also been studied as possible mood stabilizers, given their effectiveness and the lower incidence of side-effects observed, mainly with epileptic patients, who are widely experienced users of them. Among these agents, only lamotrigine has been authorized in this psychiatric disorder, basically for the prevention of depressive episodes in patients with bipolar disorder (Bowden et al., 2003; Calabrese et al., 2003). On the other hand, the clinical introduction of atypical antipsychotics renewed the interest in therapeutic research in the different phases of bipolar disorder (Vieta, 2003). Moreover, their widespread use in schizophrenia contributed reliable evidence for the fact that they were safer than conventional neuroleptics, especially in relation to extrapyramidal effects. Consequently, olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole have attained approval by the Food and Drug Administration (FDA) and other international regulatory agencies for their prescription in the treatment of manic episodes. Furthermore, olanzapine and aripiprazole have been authorized for the prevention of relapses in patients with bipolar disorder whose manic episode previously responded to treatment with these antipsychotics.

Thus, since 1993, with the clinical introduction of the new anticonvulsants and antipsychotics, the treatment of bipolar disorder has advanced considerably (Wang et al., 2003), and this has undoubtedly translated into a considerable increase in the amount of scientific literature on bipolar disorder — as it has been analyzed in this study. Nevertheless, despite the large quantity of reviews published in recent years on clinical, diagnostic, epidemiological and other aspects of bipolar disorder (Bauer and Pfenning, 2005; De Lima et al., 2005, Vieta, 2005), as well as studies on the relevant therapy (Wang et al., 2003; Malhi et al., 2003), to date there have been no rigorous studies, save certain attempts (Clement et al., 2003), aimed at assessing the growth of scientific production in relation to this pathology.

Bibliometric studies, despite their methodological limitations, are useful tools for assessing the social and scientific relevance of a given discipline or field (Bordons and Zulueta, 1999), in that they permit an overview of the growth, size and distribution of the scientific literature on the area, over a particular time period (López-Piñero and Terrada, 1992a,b). We therefore decided to carry out the present bibliometric analysis on the publications related to bipolar disorder and its pharmacological treatment, as well as its evolution over the period 1980–2004.

2. Methods

The databases used in this bibliometric study were MEDLINE (Index Medicus, U.S. National Library of Medicine, Bethesda, MD, United States) and Excerpta Medica (EMBASE) (Elsevier Science Publishers,

Table 1
Search strategy

"Bipolar spectrum"	Therapeutic groups	Drugs
*Bipolar disorder**	*Antimanic**	*Aripiprazole*
Bipolar illness	*Mood stabiliz**	*Carbamazepine*
*Bipolar patient**	*Mood regulat**	*Clozapine*
Bipolar spectrum	*Mood normaliz**	*Felbamate*
*Bipolar mani**	*Antipsychotic**	*Gabapentine*
*Bipolar depress**	*Neuroleptic**	*Lamotrigine*
*Manic–depressive**	*Antiepileptic**	*Levetiracetam*
Rapid cycling	*Anticonvulsant**	*Lithium*
		Olanzapine
		Oxcarbazepine
		Quetiapine
		Risperidone
		Sertindole
		Tiagabine
		Topiramate
		*Valpro**
		Vigabatrine
		Ziprasidone

MEDLINE and EMBASE databases (1980–2004).

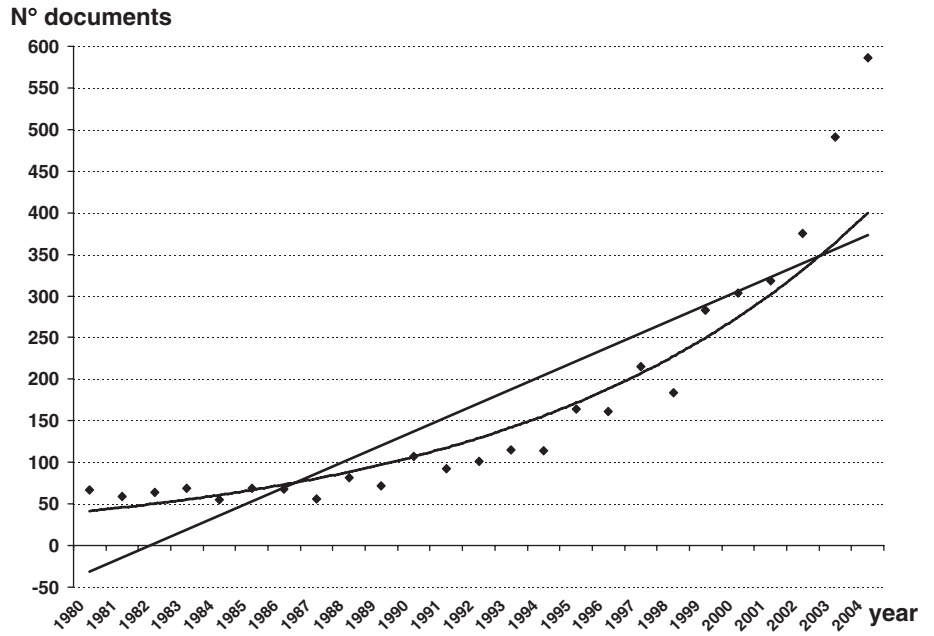

Fig. 1. Growth of scientific production in bipolar disorder. A linear adjustment of the data was carried out, and a fitting to an exponential curve, in order to check whether production follows Price's Law of exponential growth. Linear adjustment: $y=16.872x-48.53$ ($r^2=0.7367$). Exponential adjustment: $y=37.929e^{0.0942x}$ ($r^2=0.9019$).

Amsterdam, Netherlands), which are considered the most exhaustive databases in the biomedical field, and which both participate in the OVID system (Ovid Technologies Inc., New York, United States).

Using remote downloading techniques, we selected documents containing, in the TI (title) section, the descriptors *bipolar disorder**, *bipolar illness*, *bipolar patient**, *bipolar mani**, *bipolar depress**, *bipolar*

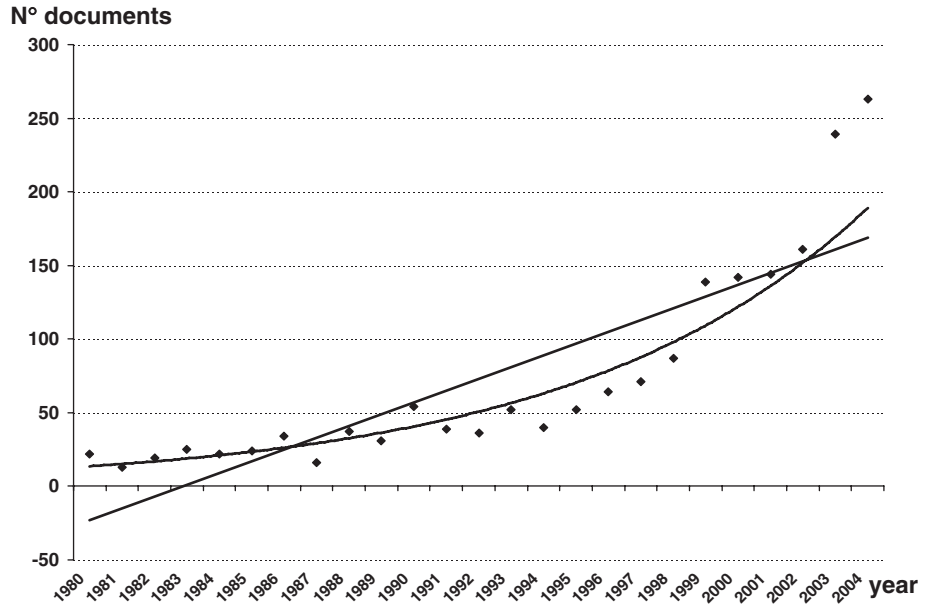

Fig. 2. Growth of scientific production on pharmacological treatment of bipolar disorder. A linear adjustment of the data was carried out, and a fitting to an exponential curve, in order to check whether production follows Price's Law of exponential growth. Linear adjustment: $y=7.9869x-30.79$ ($r^2=0.7214$). Exponential adjustment: $y=12.169e^{0.1097x}$ ($r^2=0.8985$).

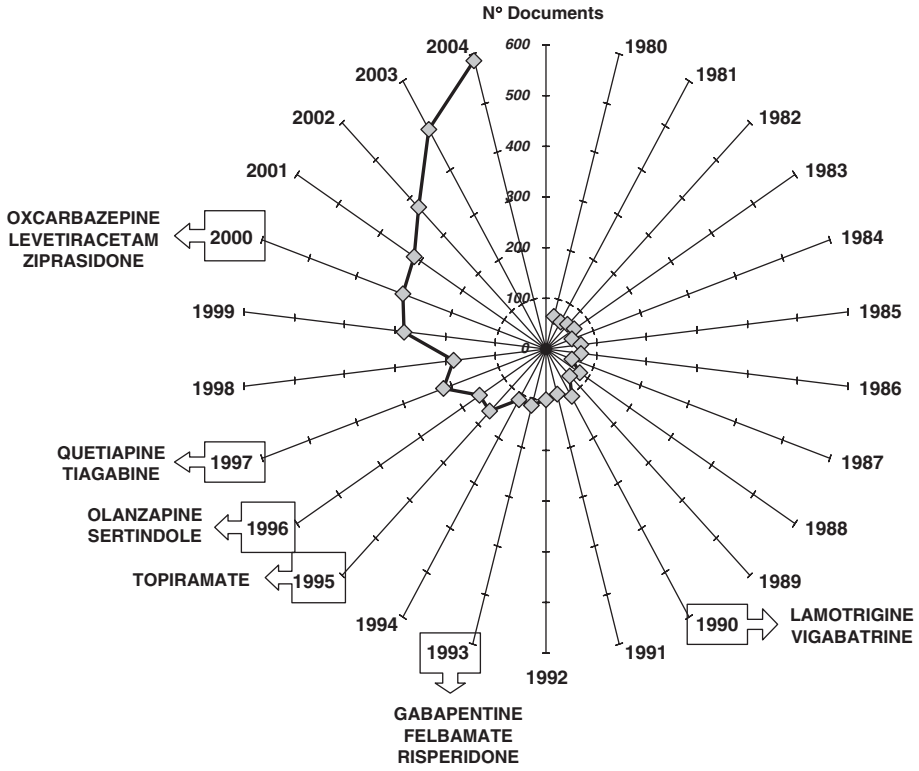

Fig. 3. Number of documents on bipolar disorder (1980–2004) and international authorization of anticonvulsants and antipsychotics.

spectrum, *manic–depressive**, and *rapid cycling*, and always for documents published between 1980 and 2004. The rest of the descriptors, referring to pharmacological aspects, were not restricted to any field of the database. The search criteria are shown in Table 1. For the purposes of this study we considered all the original articles, brief articles, reviews, editorials, letters to the editor, etc., and all duplicated documents were

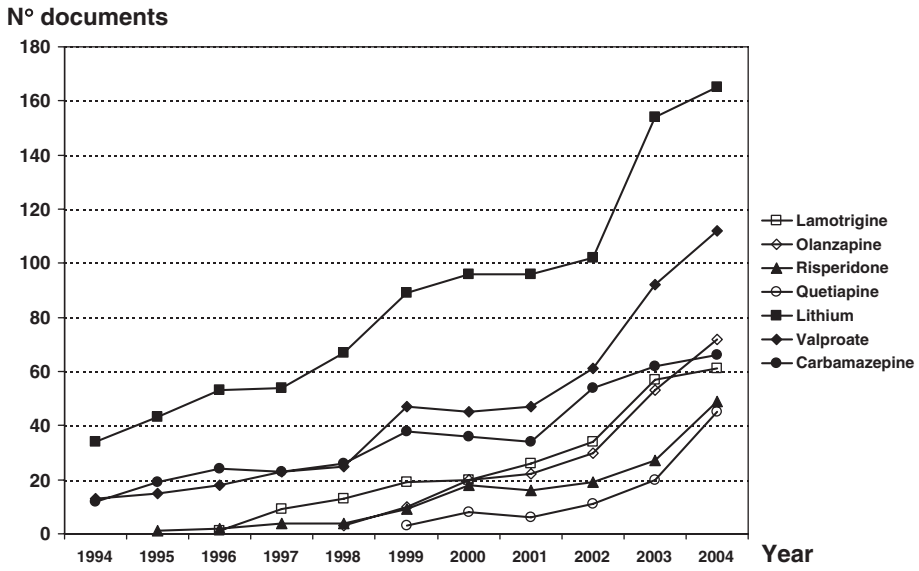

Fig. 4. Evolution of documents on drugs authorized for bipolar disorder (MEDLINE and EMBASE: 1994–2004).

eliminated. In this regard, the OVID system permits the elimination of items that may be duplicated in each of the databases (MEDLINE and EMBASE).

Among the bibliometric indicators of production applied is Price's Law (Price, 1963). This law, without doubt the indicator most widely used in analysis of the productivity of a specific discipline or a particular country, reflects a fundamental aspect of scientific production, which is its exponential growth. This phenomenon implies a faster pace of growth for science than for the rest of human activities, so that its size would duplicate every 10–15 years. In order to assess whether the growth of scientific production in bipolar disorder follows Price's Law of exponential growth, we made a linear adjustment of the data obtained, according to the equation $y=16.872x-48.53$, and another adjustment to an exponential curve, according to the equation $y=37.929e^{0.0942x}$.

Another indicator included in the present analysis is the national participation index (PI) for overall scientific production. The PI reflects the ratio of the number of documents generated by a given country and the total number of documents obtained in the repertoire. Likewise, the PI has been correlated with some social and health data for each country, such as number of physicians or total per capita expenditure on health, data that is obtained from the World Health Organization website (http://www.who.int/country/es). PI in bipolar disorder has also been compared with global PI in biomedical and health sciences (as well as for psychiatry in particular) for the world's 20 most productive countries in the period 1994–2002, according to the results from Camí et al. (2005).

3. Results

After study of the journals analyzed, during the period 1980–2004, we obtained 4270 original documents (articles, reviews, editorials, letters to the editor, etc.) dealing with different aspects related to bipolar disorder. Of these, 1825 correspond to drug therapy: lithium (1351), valproate (544), carbamazepine (493), lamotrigine (240), olanzapine (210), risperidone (149), clozapine (117), topiramate (111), quetiapine (93), ziprasidone (55), oxcarbazepine (51), aripiprazole (37), tiagabine (24), and others (19).

As can be seen in Fig. 1, over the last 25 years there has been a marked increase in the number of publications generated in relation to bipolar disorder at a worldwide basis. The mathematical adjustment to an exponential curve, shown in Fig. 1, permits us to obtain a correlation coefficient $r=0.9479$, indicating 9.81% of variance unexplained by this fitting. In contrast, the linear adjustment of the measured values provides an $r=0.8493$, and

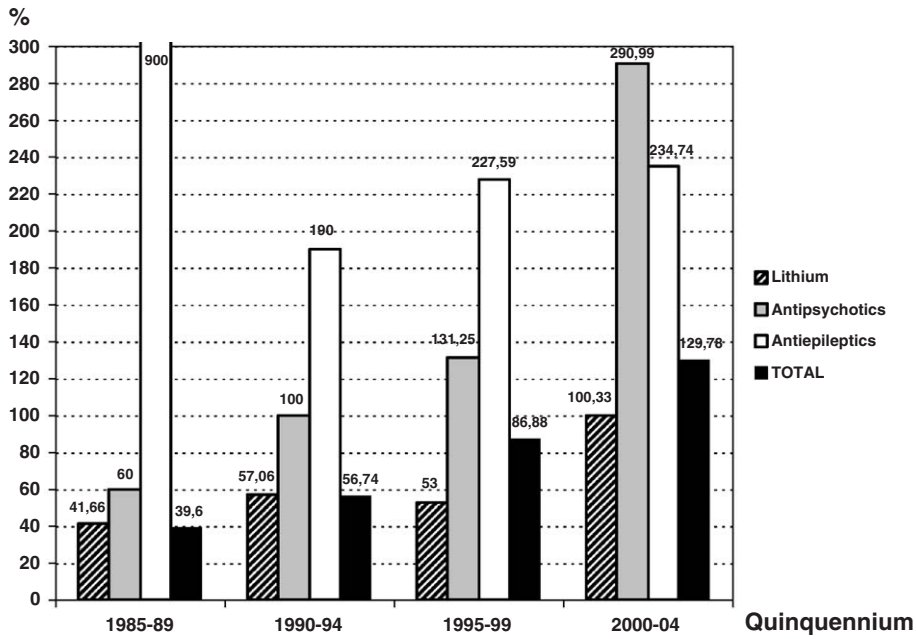

Fig. 5. Cumulative growth by five-year periods of scientific production on lithium, antipsychotics, antiepileptics and total pharmacotherapy for bipolar disorder. Data from each five-year period refer to evolution over the previous period. The period of reference is 1980–1984. Data expressed in percentages.

therefore a percentage of unexplained variance of 26.33%. With these data we can conclude that the repertoire analyzed is more in keeping with an exponential fitting than a linear one, and that the postulates of Price's Law are fulfilled. Likewise, carrying out a similar exercise but considering solely the documents specific to drug therapy (Fig. 2), the results for this field also fall into line with Price's Law of exponential growth ($r=0.9479$ in the exponential adjustment — unexplained variance of 10.15% — vs. $r=0.8494$ in the linear adjustment — unexplained variance of 25.86%).

The clinical introduction of the new anticonvulsants and antipsychotics in different countries of the world, especially since 1994, appears to have contributed substantially to the increase in scientific production in the field of bipolar disorder, as can be seen in Fig. 3. Starting out from that year, we illustrate in Fig. 4 the evolution that has occurred in the last decade of the literature on all the drugs approved for treatment of bipolar disorder. With effect from 1999, the growth is manifest, due mainly to the new drugs, and does not appear to saturate, except in the case of carbamazepine. The increase in publications on lithium and valproate may be due, in a secondary manner, to the appearance of studies on the new drugs that use these classic agents for comparative purposes.

Fig. 5 illustrates the matter even better. Analyzing the last 20 years, it can be seen that cumulative growth in total scientific production related to bipolar disorder in each five-year period over the previous one even gradually increases. Notable in this respect is the rate of accumulated growth of the new antiepileptics in the period 1990–94, after discarding the artefact of the previous five-year period (only one article in the period 1980–84). In contrast, in the period 2000–04, the greater accumulated growth corresponds to the new antipsychotics.

Among the countries generating research on bipolar disorder, the most significant, as Table 2 shows, is the United States, whose PI is 44.2, followed by the United Kingdom (PI=14.4), Netherlands (PI=9.1), France (PI=4.1), Denmark (PI=3.8) and Sweden (PI=3.2). However, if we consider the productivity of these countries in this area in relation to their overall production in the field of psychiatry, only 7 (Denmark, Netherlands, Brazil, France, Switzerland, Sweden and the United Kingdom) of the 20 largest producers in biomedicine and health sciences (in the period 1994–2002) devote a

Table 2
Distribution of documents on bipolar disorder and pharmacotherapy in the world's most productive countries in biomedicine and health sciences, for the period 1980–2004

	Country[a]	%[a]	Psychiatry[b] (%)	BD	Lithium	Classical AEDs	New AEDs	Antipsychotics
				n (%)				
1	USA	41.37	49.12	1886 (44.2)	574	313	126	281
2	UK	10.68	14.29	616 (14.4)	201	91	34	91
3	Japan	8.73	1.46	61 (1.4)	12	4	0	4
4	Germany	8.03	6.42	135 (3.2)	60	35	19	39
5	France	5.85	2.81	174 (4.1)	54	34	7	25
6	Canada	4.95	7.13	93 (2.2)	39	20	7	17
7	Italy	4.41	2.21	29 (0.68)	9	6	2	5
8	Netherlands	3.21	3.22	389 (9.1)	93	39	15	42
9	Australia	2.89	4.97	52 (1.2)	29	15	4	6
10	Sweden	2.60	2.59	137 (3.2)	41	17	11	17
11	Spain	2.41	1.15	48 (1.12)	14	9	3	11
12	Switzerland	2.00	1.57	90 (2.1)	33	12	9	7
13	Belgium	1.48	0.75	8 (0.19)	4	1	0	1
14	Israel	1.33	2.09	8 (0.19)	5	0	0	0
15	Finland	1.26	1.79	7 (0.16)	1	0	0	1
16	Denmark	1.26	1.32	163 (3.8)	54	22	14	24
17	China	1.07	0.62	19 (0.44)	5	2	0	1
18	Austria	1.05	0.77	12 (0.28)	3	1	1	3
19	India	0.93	0.55	7 (0.16)	5	0	0	0
20	Brazil	0.87	0.43	31 (0.72)	9	8	4	4

BD (bipolar disorder), AED (antiepileptic drug).
[a]The world's 20 most productive countries in biomedicine and health sciences for the period 1994–2002, and [b]their productivity in the discipline of psychiatry.
Data from Camí et al. (2005) (http://193.147.240.216/webs/MapaBiomedico2002/Index.htm).

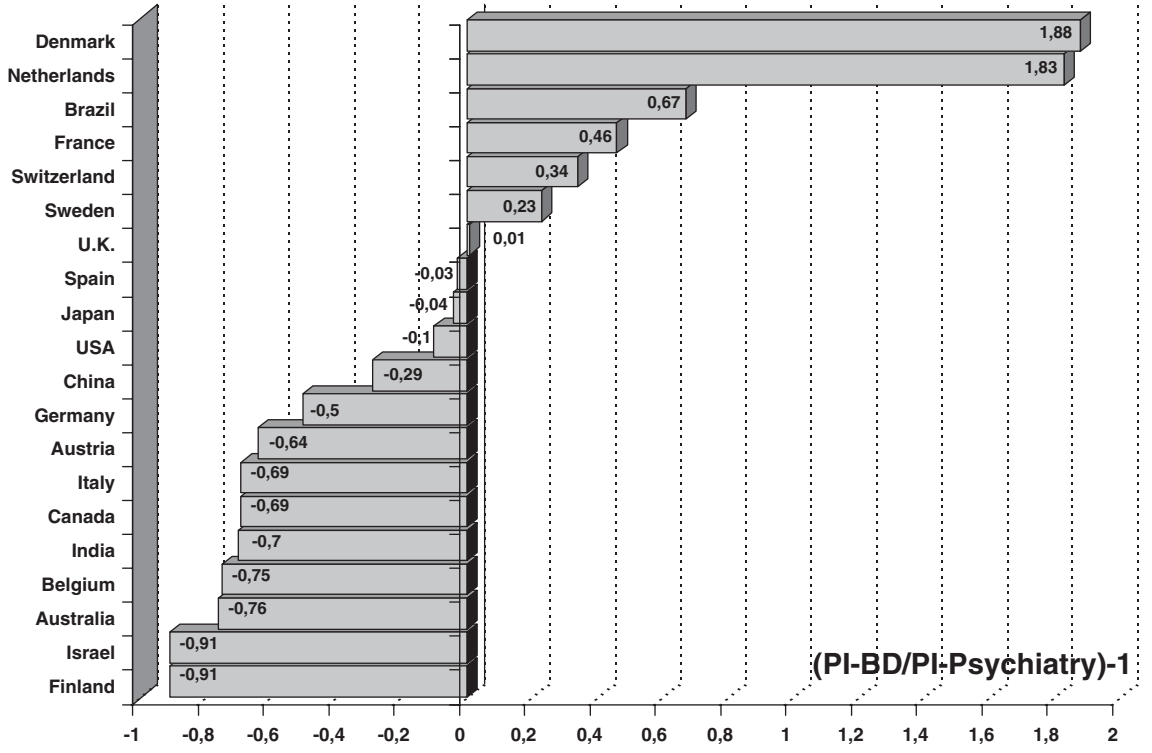

Fig. 6. Relationship between production of scientific literature on bipolar disorder and total production in the field of psychiatry in the world's 20 most productive countries in biomedicine and health sciences. PI (participation index), BD (bipolar disorder). Data on total scientific production in psychiatry for the 20 countries correspond to the period 1994–2002, and were taken from Camí et al. (2005) (http://193.147.240.216/webs/MapaBiomedico2002/Index.htm).

higher percentage of attention to the study of bipolar disorder (Fig. 6). Table 2 also shows the number of documents contributed by each group of agents used in the treatment of bipolar disorder (lithium, classical antiepileptics, new antiepileptics and atypical antipsychotics), in the 20 countries most productive in biomedicine.

In the analysis of the correlation between PI and the per capita health expenditure of each of the countries with the highest scientific production in health sciences, the distribution obtained is quite similar, except for a few fairly numerically irrelevant exceptions, such as Brazil and China (Fig. 7). On the other hand, if we carry out the same type of analysis versus the total number of physicians in each country (as an indicator of the most representative professional group in clinical research), the results obtained confirm that the best-placed countries are Denmark, Netherlands and the United Kingdom (Fig. 7).

4. Discussion

Bibliometric studies constitute interesting tools for assessing the social and scientific importance of a given discipline over a specific time period (López-Piñero and Terrada, 1992a,b). Despite their methodological limitations, these analyses permit an overview of the growth, extent and distribution of the scientific literature related to a particular discipline, and the study of the evolution of not only the biomedical speciality, field of specialization or issue in question, but also the scientific production of an institution, country, author or research group (Bordons and Zulueta, 1999). The term "bibliometrics" was introduced in 1969 by Alan Pritchard, to define the application of mathematical and statistical methods to the process of dissemination of written communication in the area of scientific disciplines, by means of quantitative analysis of the different aspects of this type of communication (Pritchard, 1969).

Previous bibliometric studies have drawn attention to a series of limitations characteristic of this sociometric approach (Gómez and Bordons, 1996), since it is obvious, for example, that the international scientific production in a particular field, such as bipolar disorder in this case, is much more extensive. However, the criteria set by the databases themselves condition the subsequent development of the material to be studied. For instance, many

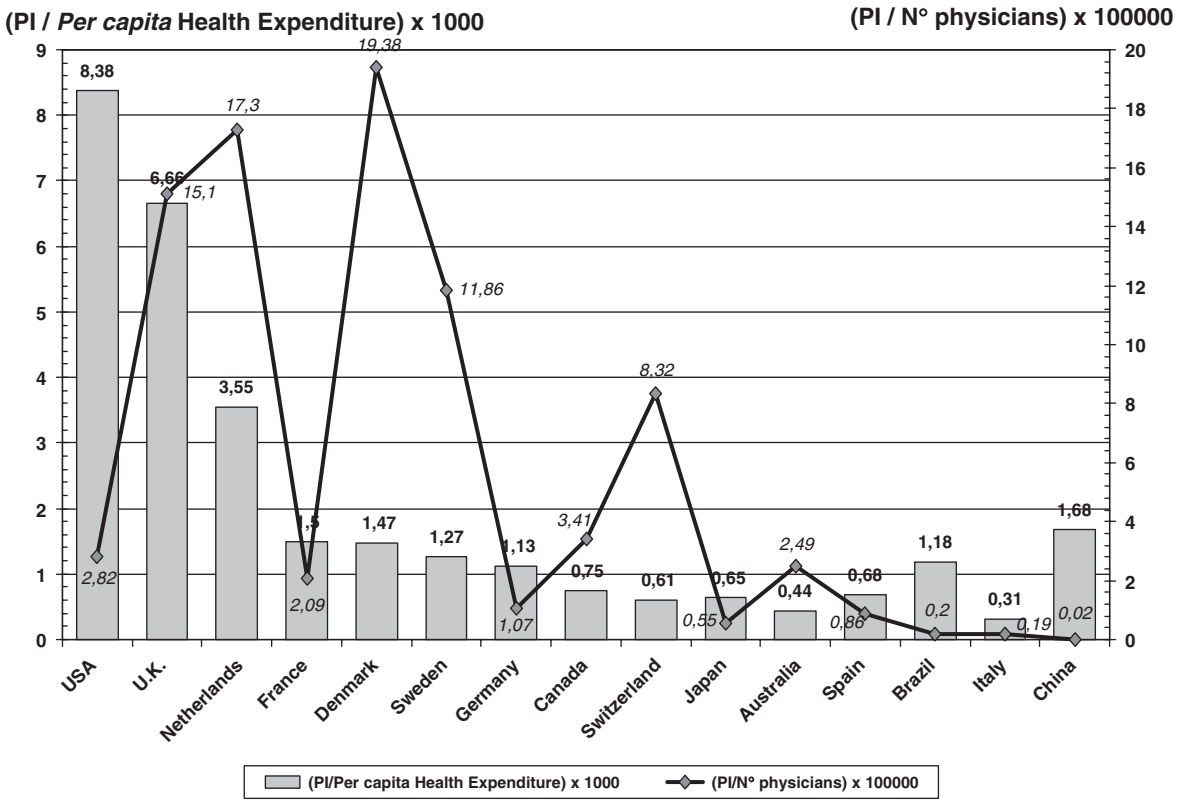

Fig. 7. Relationship between production of scientific literature on bipolar disorder and per capita health expenditure and number of physicians, in the world's 15 most productive countries in biomedicine and health sciences. PI (participation index). Data on scientific production of the 15 countries, for the period 1994–2002, were taken from Camí et al. (2005) (http://193.147.240.216/webs/MapaBiomedico2002/Index.htm), and the data on health economics and health personnel from the World Health Organization website (2005) (http://www.who.int/country/es/).

journals are not indexed in the usual databases; this is also the case of contributions made to scientific conferences and meetings (López-Muñoz et al., 1996). Nevertheless, the recognized quality of the publications included in the databases employed in the present study and their coverage means that the documents selected constitute a more than representative sample of the international research on the area in question.

Taking into account these premises, the design of the present analysis allows us to make a global assessment of the growth of scientific literature in relation to bipolar disorder and its pharmacological treatment. In this regard, it should be stressed how, as Fig. 1 shows, the number of publications on bipolar disorder has undergone exponential growth over the last 25 years, and especially after 1994, without evidence, up to the end of the period studied, of the process of saturation postulated by Price in his theory of expansion of scientific literature (Price, 1963). This great increase coincides clearly with the publication of the study by Bowden et al. (1994) in the *Journal of the American Medical Association* demonstrating the effectiveness of valproate (superior to placebo and similar to lithium), and with the commercialization of this drug in the United States.

The enormous growth in the scientific literature in this area leads us to the conclusion that the field of bipolar disorder is one that is in the prime of development from the clinical and basic research perspective. Previous studies by our group have reflected a comparable situation in the general area of psychiatry and of neuroscience (López-Muñoz and Rubio, 1995; López-Muñoz et al., 1996). Some authors, however, also applying bibliometric tools, have reported the research activity in the field of bipolar disorder as inferior to that of other fields of psychiatry, such as schizophrenia (Clement et al., 2003), suggesting a possible greater capacity for future development. In this regard, it has been argued that bipolar disorder has not so far received sufficient attention from the relevant academics and institutions (Morriss et al., 2002).

Although manic–depressive illness ("folie circulaire") has been reported and described since the mid-nineteenth century as specific psychiatric disorders, it was not until relatively recently that bipolar disorder

began to receive the scientific and social recognition it currently enjoys (Del Porto, 2004). Among the factors that may have contributed to this situation of "scientific neglect" compared to other psychiatric disorders, such as major depression or schizophrenia — in addition to the scarce knowledge of its etiopathogeny and the underestimation of its prevalence figures — we must consider the state of therapeutic pseudo-orphanhood that existed until practically a decade ago. Indeed, until the mid-1990s, when the antimanic efficacy of valproate was proven, the only pharmacological tool available for the treatment of these patients was lithium. Clement et al. (2003) also suggest that the attraction of research on bipolar disorder may have been adversely affected by the clinical perception of the lesser seriousness of the illness compared to other psychiatric pathologies, perhaps more stimulating, such as schizophrenia. These authors also stress that bipolar patients, given the cyclic condition of their illness, do not make ideal patients for researchers, with regard to either recruitment or durability in studies. The appearance in 1999 of a specific scientific journal for this area, *Bipolar Disorders*, may mark the beginning of a new era in research and development related to this psychiatric pathology.

The scientific literature on the pharmacological tools employed with bipolar disorder, according to our data, has also grown considerably in these last 25 years, and in an exponential way (Fig. 2), above all from the period 1990–94 onwards, coinciding with the clinical introduction of new pharmacological agents in different countries of the world. Furthermore, there is another important upsurge in the most recent five-year period (2000–04), coinciding with the period of clinical development immediately prior to official approval of the new antiepileptics and antipsychotics in bipolar disorder, which culminated in the authorization of risperidone by the FDA in 2003, followed by those of lamotrigine, olanzapine, quetiapine, ziprasidone and aripiprazole in the United States, European Union and elsewhere. It is the period 2000–04 that sees the greatest increase in scientific production on these drugs over the previous five-year period (290.99% in the case of the new antipsychotics, 274.74% for the new anticonvulsants, and even 100.33% in the case of lithium), as can be seen in Fig. 5. Likewise, there is a close correlation between the increase observed in the number of documents on bipolar disorder and pharmacological treatment of the condition. In the individual analysis of the new drugs authorized for prescription in bipolar disorder, lamotrigine emerges as the agent most widely studied, both from the clinical and safety points of view, as shown by the present bibliometric study, though in the final years of the analysis, the drug showing the most growth has been olanzapine, which even surpassed lamotrigine in 2004.

With regard to the PI of the different countries in scientific production on bipolar disorder, it should be borne in mind, first of all, that the databases normally used in this type of analysis, as is our case with MEDLINE and EMBASE, only include in their AD section (*address of authors*) the address of the first signatory or corresponding author. Thus, the PIs of the different countries reported in this study will always be an approximation, to the places in which research on bipolar disorder is generated, generally a fairly faithful one, but not totally accurate. The small variations with respect to the reality will be determined by the presence of collaborative projects between research groups from different countries (multi-centre and multinational clinical trials, etc.). The two major Anglophone countries, United States and United Kingdom, head the ranking of producer countries, and between them generate over half the total scientific production in this field (58.6%). The fact that in these two countries are home to the pharmaceutical companies responsible for the development of the new agents approved for bipolar disorder (lamotrigine — GlaxoSmithKline, UK, olanzapine — Eli Lilly, USA, risperidone — Janssen Pharmaceutica, USA, quetiapine — AstraZeneca, UK, ziprasidone — Pfizer, USA, and aripiprazole — Bristol-Myers Squibb/Otsuka Pharmaceutical Co., USA/Japan) may help to explain this high PI.

Table 2 shows the data from the 20 most productive countries in biomedicine and health sciences, according to a recent study published by Camí et al. (2005), and compares the data for general productivity in the psychiatry discipline with productivity in the specific field of bipolar disorder. It is worthy of note how some places, such as Netherlands, Denmark, Sweden, France, Switzerland or Brazil, sit near the top of the ranking for bipolar disorder production (see also Fig. 6), reflecting the special interest of these countries in research into this pathology. Other countries, such as the United Kingdom, Spain, Japan and United States, maintain rates of productivity in bipolar disorder research that are in proportion with their global index for psychiatry. At the other side of the scale, it is interesting to note the lower relative interest in this disorder, within the context of their general production in psychiatry, of countries such as Germany, Italy or Canada.

The correlation of scientific production in bipolar disorder with the per capita health expenditure of each country, shown in Fig. 7, offers us a parallel view of this phenomenon; in general, there is confirmation of the

notion that the higher the spending on health, the greater the research production. In this regard, it should be made clear that a country's scientific production in a given field tends to reflect a science research and development policy begun some years prior to the period analyzed, and is not the fruit of particular economic circumstances. Likewise, when analysis is carried out versus the total number of physicians in the country, as an index of the professional group directly related to clinical research, countries such as Denmark, Netherlands, United Kingdom, Sweden and Switzerland also emerge at the head of the rankings; it is striking, however, to observe the low ratios of countries such as United States, France, Germany or Japan.

Finally, and by way of conclusion, it can be asserted that, despite the limitations characteristic of bibliometric studies, and thanks to the design of this study, we have been able to offer a picture of the representativeness and evolution of international research on bipolar disorder, observing the parameters of quality and dissemination most commonly employed at an international level. Research in this field will possibly continue to grow in the coming years, bearing in mind that the ideal mood stabilizer has not yet been found. Although, classically, euthymizers, thymoregulators and mood regulators have been defined as pharmacological agents effective in the manic and depressive phases of bipolar disorder, this definition is far from complete, since these drugs should also act to modify the patient's vulnerability to suffering future episodes of depression or mania, to prevent recurrences and relapses (Sachs, 1996; Bowden, 2002). These therapeutic aspects therefore, together with the great unknowns in relation to the etiopathogeny of the illness, guarantee a promising future for research on bipolar disorder.

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