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BIBLIOMETRIC ANALYSIS OF BIOMEDICAL PUBLICATIONS ON SSRIs DURING 1980–2000

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We performed a bibliometric study of the scientific publications referring to selective serotonin reuptake inhibitors (SSRIs). The database used was EMBASE: Psychiatry. We applied the principal bibliometric indicators: Price's and Bradford's laws on the increase or dispersion of scientific literature, Lotka's law on the productivity of authors, the participation index (PaI) of countries, the productivity index (PI) of authors, and the collaboration index. By means of manual coding, documents were classified according to type of study and to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or nonpsychiatric categories. We analysed 3,622 original documents published between 1980 and 2000. Our results show nonfulfilment of Price's law because production on SSRIs does not grow exponentially ($r = 0.937$ vs. $r = 0.946$, after linear adjustment). The journal most employed is the Journal of Clinical Psychiatry (Bradford's first zone). The United States is the most productive country (PaI = 41.50). The documents were distributed in four groups: experimental pharmacology (8.38%), tolerance and safety (34.94%), clinical efficacy (49.11%), and not specified (7.56%). The drug most studied was fluoxetine (1,745 articles), followed by paroxetine (659). The DSM-IV diagnostic categories most studied were depression (834), obsessive–compulsive disorder (171), and panic disorder (75). The control antidepressants most used in comparative clinical studies were amitriptyline (51) and imipramine (42). The results of the present study show that the SSRIs are not solely antidepressant drugs, but also have a wide range of uses both within the psychiatric sphere (especially in the field of anxiety) and outside it, which explains the considerable scientific production generated in relation to these drugs. Depression and Anxiety 18:95–103, 2003. © *2003 Wiley-Liss, Inc.*

Key words: *SSRIs, antidepressants, anxiolytics, bibliometry*

INTRODUCTION

The psychopharmacology revolution of the 1950s introduced several groups of psychopharmacological agents. These psychotropic drugs, such as neuroleptics, tricyclic antidepressants (TCAs), and benzodiazepines, are still used in everyday clinical practice. With respect to the treatment of depressive patients, TCAs substantially modified the therapeutic approach, contributing to a reduction in the suffering of patients previously treated with archaic and dangerous biological therapies, often in conditions of institutionalization. In the mid-1980s, a new group of antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs), appeared

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TABLE 1. Clinical development of SSRIs*

	Company	Patent data		Phase I trials		Launch	
Fluvoxamine	Solvay	1975	Netherlands	Jan 1978	Netherlands	1983	Switzerland
Fluoxetine	Lilly	1974	USA		USA	1986	Belgium
Citalopram	Lundbeck	1977	UK	Feb 1979	Denmark	Jun 1989	Denmark
Sertraline	Pfizer	1979	USA	Apr 1984[a]	USA	Nov 1990	UK
Paroxetine	Novo Nordisk	1973	UK	Feb 1983	Denmark	Feb 1991	UK

*Modified from López-Muñoz et al. [1998a].
[a]Preclinical trials data.

(Table 1). These agents have notably improved the quality of life of depressive patients and are currently considered the best therapeutic alternative to the classic tricyclics [López-Muñoz et al., 1998a]. Direct and indirect consequences of the introduction of these drugs (fluvoxamine, fluoxetine, paroxetine, sertraline, and citalopram) have been multiple, affecting different areas of the social health context. Perhaps the consequence with the greatest relevance is the introduction of primary care in the area of mental health, which has contributed decisively to weakening the stigmatization traditionally accompanying psychiatric attention.

This new therapeutic alternative is founded on antidepressant efficacy rates comparable to those obtained with TCAs and its undoubted advantages from the safety profile perspective, the clinical perspective (new therapeutic indications), and in relation to practical aspects (one administration per day), which have substantially modified prescription habits [De Vane, 1994; Muller and Volz, 1996; López-Ibor et al., 1999; López-Ibor et al., 2000], giving rise to considerable growth in the use and consumption of antidepressants [Johnson et al., 1997; Henry and Rivas, 1997; López-Muñoz et al., 1998b].

In the same way that the consumption of serotonergic antidepressants has seen enormous growth, so has the scientific literature in relation to these drugs, a circumstance that has motivated the present bibliometric analysis. Bibliometric studies are interesting tools for assessing the social and scientific importance of a specific discipline, during a given period. Despite their methodological limitations, these analyses permit us to examine the growth, size, and distribution of the scientific literature related to a given discipline and to study the evolution of the biomedical speciality, the area of specialization or the subject in question, and the scientific production of an institution, country, author, or working group.

In two previous communications by our group [Alamo et al., 1996a,b], we offered data on some bibliometric indicators about publications referring to SSRIs during 1980–1994. The aim of the present work is to complete the preliminary results obtained, through the analysis of international bibliographic production on SSRIs during 1980–2000 and discussion and interpretation of the circumstances affecting its development.

MATERIALS AND METHODS

DATA SOURCE

The database employed in the present bibliometric study was *Excerpta Medica* (EMBASE) (Elsevier Science Publishers, Amsterdam, The Netherlands), considered one of the most exhaustive databases in the biomedical field. As a complement, with the aim of introducing data not included in EMBASE, we also used the database MEDLINE (*Index Medicus*, U.S. National Library of Medicine, Bethesda, MD). Both are on CD-ROM (SilverPlatter Information, Inc., Norwood, MA). EMBASE CD: Psychiatry includes references from 3,500 journals from across the world (published in 110 countries), 60 of which are considered priority journals, being analyzed cover to cover. Through teledischarge techniques, we selected documents that contained, in the TI (title) section, the descriptors *fluvoxamine*, *fluoxetine*, *paroxetine*, *sertraline*, or *citalopram*, and always restricting ourselves to documents published between 1980 and 2000.

BIBLIOMETRIC INDICATORS

As a methodological basis in developing the analysis of the results, we applied a series of bibliometric models and indicators considered as referential. For bibliometric indicators of production we applied Price's law [Price, 1963]. This law, undoubtedly the indicator most commonly used when the aim is to analyze productivity in a specific discipline or a given country, reflects an essential fact of scientific production, which is its exponential growth. This phenomenon supposes a faster pace of growth for science production than for the rest of human activities, so that its size would duplicate every 10–15 years. To assess whether the increase in data conforms to Price's law of exponential growth, we carried out a linear adjustment of the values and another adjustment to an exponential curve.

With respect to the productivity of researchers, Lotka's law [Lotka, 1926] aims to calculate the number of authors expected for a given number of works produced. This law is expressed as: $An = Kn^{-b}$, $n = 1, 2,$

3,…, where *An* represents the probability that an author produces *n* publications on a given topic, whereas *K* and *b* are parameters to be estimated according to the data. Following this law, as long as the time studied is sufficiently long and the bibliographical search as complete as possible, "the number of authors that publish *n* works is inversely proportional to n^2." With regard to this aspect, we calculated the productivity index of the authors (PI). The PI (logarithm of the values of *n* for each author) allows us to establish three levels of productivity: PI = 0 (transience index; authors with a single publication—that is, occasional authors), $0 < PI < 1$ (authors that have published between two and nine articles) and $PI \geq 1$ (highly productive authors, with ≥ 10 articles).

As a bibliometric indicator of dispersion of scientific information we used Bradford's law [Bradford, 1948]. To know the distribution of the scientific literature of a given discipline, Bradford proposed a model of concentric zones of productivity (Bradford's zones) with decreasing density of information. Thus, each zone would contain a similar number of articles, but the number of journals in which these were published would increase on moving from one zone to another. This model thus permits us to determine which journals are most used or have a greater specific weight in a given area or in scientific production. Thus, the number of journals in the different Bradford zones would be: *1*, *n*, n^2,…. Among the indicators of the repercussion of the publications, we used the impact factor (IF). This index, developed by the Institute for Scientific Information (Philadelphia, PA), is published annually in the section *Journal Citation Reports* (JCR) 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 2 previous years and the total number of articles published by the journal in question in these 2 years. The JCR lists scientific journals by specific areas, ascribing to each of them their corresponding IF and establishing a ranking of prestige.

Other indicators included in the present analysis were the index of collaboration between authors (signatures/document or authors/paper index), and the participation index (PaI). The PaI shows the quotient between the number of papers generated in a country or institution and the total number of documents collected in this repertoire. Likewise, this PaI has been related with some health data of each country, such as the number of physicians and the total health expenditure per capita, obtained from the World Health Organization Web page (http://www.who.int/country/es).

DOCUMENT ALLOCATION

Through manual coding and after analysis of the title and/or abstracts of the articles, they were ascribed to four groups: experimental pharmacology, clinical efficacy, tolerance and/or safety, and a fourth group of articles that could not be classified in any other group ("not specified"). Likewise, the subgroup of articles with clinical content was classified according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic categories, and, where applicable, according to the nonpsychiatric pathology that was the object of study. Furthermore, we coded the control agent in the clinical studies with controlled design.

RESULTS

We obtained, after the study of the journals analyzed for 1980–2000, 3,622 original articles dealing with different aspects of research on the SSRIs. Of these, 1,745 correspond to fluoxetine, 659 to paroxetine, 539 to fluvoxamine, 516 to sertraline, and 332 to citalopram. As Figure 1 shows, we found a notable increase over the past 2 decades in the number of publications on the SSRIs. Mathematical adjustment to an exponential curve ($y = 8.1338e^{0.2167x}$), as shown in Figure 1, permits us to obtain a correlation coefficient $r = 0.937$, which indicates that a 12.23% of variability remains unexplained by this adjustment. On the other hand, the linear adjustment ($y = 21.662x - 65.81$) of the measured values provides an $r = 0.946$, and therefore a percentage of unexplained variability of 10.4%. With these data, we can conclude that the repertoire analyzed, despite its growth, does not fulfil the proposals of Price's law, possibly owing to a previous saturation point. In fact, if we carry out the same exercise for the period 1980–1998, we do indeed observe a fit with Price's law of exponential growth of scientific literature for this material ($r = 0.956$ in the exponential adjustment versus $r = 0.951$ in the linear adjustment).

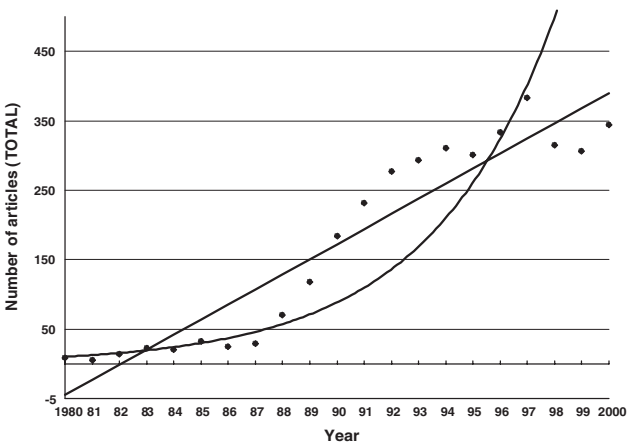

Figure 1. Increase in number of international biomedical publications on SSRIs in our documental repertory (EMBASE: Psychiatry). Linear adjustment of data and another adjustment to an exponential curve were performed to verify whether the analyzed production fits Price's law.

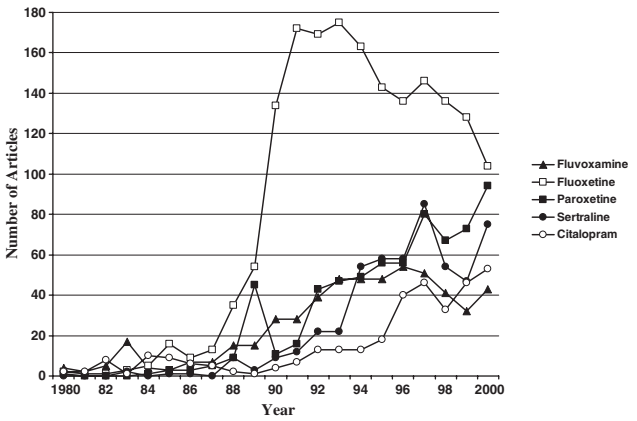

Figure 2. Annual evolution in number of documents for the five analyzed drugs (fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram).

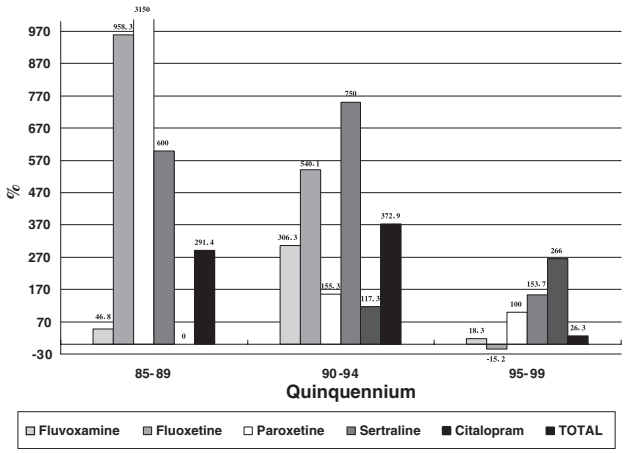

Figure 3. Quinquennial accumulative increase in the SSRIs scientific production for the six studied groups. Data for each quinquennium refer to evolution over the preceding one. The initial reference quinquennium is 1980–1984. Data are expressed in percentages.

The growth in the number of articles on SSRIs, as Figure 2 shows, is spectacular, especially after 1990, and largely owing to articles on fluoxetine. This growth is maintained until 1997, with a slight decrease in the number of publications on SSRIs in succeeding years. In the case of fluoxetine, this decrease is appreciable from 1994, although it is offset by an increase in the number of publications related to paroxetine, sertraline, and citalopram (Fig. 2). Analyzing the last three 5-year periods, we can observe that accumulative growth in total scientific production for each quinquennium on the previous one is spectacular in 1985–1989 and 1990–1994, and slows considerably in the quinquennium 1995–1999. Noteworthy in 1985–1990 is the rate of accumulated growth of fluoxetine, once the artifact of paroxetine (just two articles in 1980–1984) has been discarded. On the other hand, in 1990–1994 the greatest accumulated growth corresponded to sertraline, and in 1995–1999, to citalopram (Fig. 3).

Table 2 shows the division into Bradford zones of the material studied. The mean number of articles per zone is 291.5, although if we ignore the last zone, whose accuracy is obviously lower, the mean would be 311.27. The core or first zone is composed exclusively by the *Journal of Clinical Psychiatry*, with 312 articles (254 articles from the regular issues of the journal and 58 articles from the supplements), and the second zone by the *American Journal of Psychiatry* (282 articles). The third zone would include the *Journal of Clinical Psychopharmacology* (213) and the *International Clinical Psychopharmacology* (111). The rest of the journals analyzed are included in Zones 4–12. In total, 512 different journals have been used in the publication of the material analyzed, and it is noteworthy that a mere 10 journals account for 38.18% of the documents in the repertoire analyzed. Table 3 shows the journals most used in the diffusion of scientific literature on SSRIs, together with their corresponding IF, according to the *JCR* of 2000. Table 3 demonstrates that the base journals most used in the diffusion of work on SSRIs present high IFs (of the 21 journals most used, 15 have an IF > 2), coinciding in large part with the best placed journals in the ranking of the *JCR*, in its Psychiatry section. Within this group of most used journals, as expected, the majority correspond to publications from the ambits of psychiatry and/or psychopharmacology. Only three general pharmacology journals appear (*European Journal of Pharmacology*, *Annals of Pharmacotherapy*, and *British Journal of Clinical Pharmacology*) and one general medicine journal (*The Lancet*).

Another widely used bibliometric indicator is formulated in Lotka's law. In general terms, this law is fulfilled when less than a tenth of the authors are responsible for a third of the works. In our study, 823 authors (10.49% of the total), signatories to at least

TABLE 2. Distribution of the journals in Bradford's zones

Zone	No. of journals	No. of articles	Bradford's constants
1	1	312	
2	1	282	1.00
3	2	324	2.00
4	4	334	2.00
5	5	290	1.25
6	9	318	1.80
7	14	313	1.55
8	21	314	1.50
9	41	312	1.95
10	78	313	1.90
11	262	312	3.36
12	74	74	

Total number of journals = 512. Average number of articles = 291.5. Average number of articles, excluding the last Bradford zone = 311.27.

TABLE 3. Main journals used for diffusion of SSRIs articles in our repertory (*EMBASE: Psychiatry)*

	Journal	No. of articles	IF[a]
1	J Clin Psychiatry[b]	312	4.454
2	Am J Psychiatry	282	6.577
3	J Clin Psychopharmacol	213	5.052
4	Int Clin Psychopharmacol	111	2.076
5	Psychopharmacology	100	2.804
6	Acta Psychiatr Scand	91	1.774
7	Biol Psychiatry	74	4.269
8	Pharmacopsychiatry	69	2.681
9	Br J Psychiatry	69	4.827
10	J Am Acad Child Adolesc Psychiatry	62	3.175
11	Psychopharmacol Bull	56	2.809
12	Hum Psychopharmacol	54	1.103
13	J Affective Disord	49	1.938
14	Eur Neuropsychopharmacol	47	2.045
15	Can J Psychiatry	42	1.623
16	Eur J Pharmacol	39	2.236
17	Ann Pharmacother	35	1.868
18	Lancet	33	10.232
19	Arch Gen Psychiatry	33	11.778
20	Psychosomatics	30	1.555
21	Br J Clin Pharmacol	30	2.151

IF = impact factor.
[a]JCR [2000].
[b]Articles from regular issues (254) and supplements (58) are included.

three articles, produced 35.59% of the documents analyzed, so that the observed distribution fulfils the law. Table 4 shows the general productivity of the study according to the relationship articles/author, as well as percentages of the total of authors and authorships. The 3,622 articles included in the present study correspond to a total of 7,844 authors, in turn responsible for 13,402 authorships.

The PI (logarithm of the *n* values for each author) permits us to establish the three classic levels of productivity shown in Table 5. There are 96 authors with a PI $\geq$ 1, and who can be considered a large producers—that is, they have published $\geq$10 articles. This small percentage of authors (just 1.22% of the total) generated 10.8% of the documents in our repertoire. On the other hand, 5,657 authors (72.12% of the total) produced just 1 article (PI = 0), which gives us a value for the transience index (percentage of publications corresponding to occasional authors) of 42.21. The three most productive authors published 44, 40, and 31 papers, respectively. With regard to type of institution, 33.3% of the total production was generated in hospital or clinical settings, 32.26% in the university environment, and 10.38% in the pharmaceutical industry. Figure 4 shows that among the countries generating research on SSRIs are the United States, whose PaI is 41.5, followed by the United Kingdom (PaI = 10.68), Italy (PaI = 6.35), France (PaI = 5.01), Germany (PaI = 4.65), and Canada

TABLE 4. Distribution of papers/authors and percentage of the total

No. of papers/ authors (*n*)	No. of authors with *n* papers (A*n*) (%)	No. of authorships (%)
1	5,657 (72.12)	5,657 (42.21)
2	1,118 (14.25)	2,236 (16.68)
3	493 (6.28)	1,479 (11.04)
4	181 (2.31)	724 (5.40)
5	119 (1.52)	595 (4.44)
6	79 (1.01)	474 (3.54)
7	40 (0.51)	280 (2.09)
8	40 (0.51)	320 (2.38)
9	21 (0.27)	189 (1.41)
10	17 (0.22)	170 (1.27)
11	13 (0.17)	143 (1.07)
12	9 (0.11)	108 (0.81)
13	12 (0.15)	156 (1.16)
14	5 (0.06)	70 (0.52)
15	5 (0.06)	75 (0.56)
16	7 (0.09)	112 (0.54)
17	6 (0.08)	102 (0.76)
18	4 (0.05)	72 (0.54)
19	3 (0.04)	57 (0.43)
20	3 (0.04)	60 (0.48)
21	2 (0.02)	42 (0.31)
22	1 (0.01)	22 (0.16)
23	3 (0.04)	69 (0.51)
25	3 (0.04)	75 (0.56)
31	1 (0.01)	31 (0.23)
40	1 (0.01)	40 (0.30)
44	1 (0.01)	44 (0.33)
Total	7,844	13,402

TABLE 5. Productivity Index of authors

Productivity index	No. of authors	% Authors	No. of articles	% Articles
PI = 0 (1 paper)	5,657	72.12	5,657	42.21
0 < PI < 1 (2–9 papers)	2,091	26.66	6,297	46.99
PI $\geq$ 1 ($\geq$10 papers)	96	1.22	1,448	10.80
Total	7,844		13,402	

PI = productivity index. The PI led to the establishment of three accepted levels of productivity: PI = 0 (transience index; fortuitous authors), 0 < PI < 1 (authors of intermediate productivity), PI $\geq$ 1 (large producers)

(PaI = 4.58). The majority language of the publications is English (90.28% of the articles), followed at a considerable distance by German (2.71%), French (2.04%), Italian (1.1%), Japanese (1.1%), Dutch (0.99%), and Spanish (0.64%). The collaboration index, indicative of the cooperation of authors in generating documents, has increased considerably, practically doubling between 1980 (2) and 2000 (4.09).

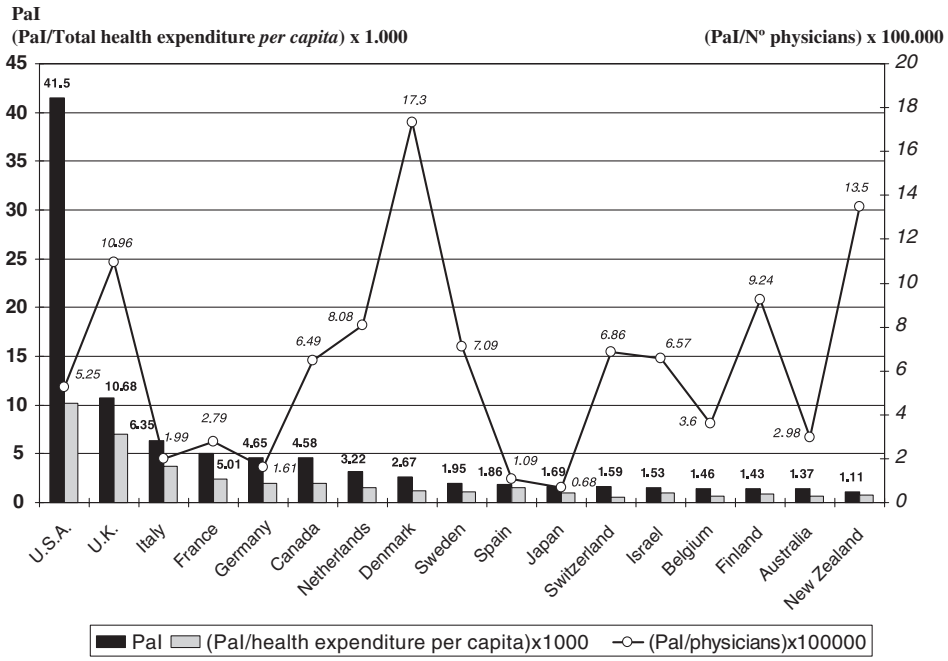

Figure 4. Countries producing biomedical literature on SSRIs, and the relation of this production to the number of physicians and the total health expenditure per capita of each country. Total number of publications with reference to the origin country is 3,072 articles. PaI = participation index. Data about health economy and human resources were obtained through the World Health Organization, 2002 (online at http://www.who.int/country/es/).

The result of the ascription of the articles, through manual coding, to the four working groups was as follows: 307 (8.38%) to the experimental pharmacology group, 1,799 (49.11%) to the clinical efficacy group, 1,280 (34.94%) to the tolerance and safety group, and 276 (7.56%) to the "not specified" group. There are no significant differences between the different drugs versus the total sample, except in the case of citalopram, which contributes a higher percentage of studies in the category of experimental pharmacology (14.78% versus 8.38% of the mean).

If we take into account only the works with clinical content, the diagnostic categories, according to DSM-IV criteria, in which the efficacy and/or safety of the SSRIs have most been assessed are mood disorders (843), anxiety disorders (323), substance abuse disorders (61), psychotic disorders (49), and eating disorders (38). With respect to the DSM-IV pathologies, the most notable are obviously those that constitute the approved indications, such as depression (834), obsessive-compulsive disorder (OCD) (171), panic disorder (75), social phobia (33), bulimia nervosa (31), generalized anxiety disorder (GAD) (22), and posttraumatic stress disorder (PTSD) (18). In other psychiatric pathologies in which the SSRIs are still not officially indicated, the number of studies is also considerable, as is the case of schizophrenia (49), alcoholism (42), trichotillomania (14), or aggresssivity (14). As regards nonpsychiatric pathologies, premenstrual syndrome constitutes an indication approved for some SSRIs, with 30 studies being obtained. Other nonpsychiatric pathologies, without official approval, in which the efficacy of the SSRIs has been studied are the dementias (20), obesity (18), and headaches/migraines (10). Among the approved indications, paroxetine is the SSRI with the greatest percentage of its global production dedicated to depression (28.07%), social phobia (2.28%), and GAD (0.76%), whereas fluvoxamine is linked most to OCD (9.28%), fluoxetine to bulimia nervosa (1.43%), citalopram to panic disorder (2.62%), and sertraline to premenstrual syndrome (1.74%) and PTSD (1.16%).

Antidepressants most frequently used in controlled and comparative studies with the SSRIs were amitriptyline (51), imipramine (42), and clomipramine (32), although there are important differences in the individual analysis of each SSRI. Thus, whereas with fluoxetine and paroxetine the drug most commonly used in comparative studies is amitriptyline, with fluvoxamine and sertraline it is imipramine, and with citalopram it is mianserine. In the comparative studies among the own SSRIs, fluoxetine constitutes the most important referent. Controlled studies with placebo numbered 221 in total.

DISCUSSION

The present study, like all bibliometric analyses, has an inherent important methodological limitation: selection of the document repertoire. In this regard,

the material selected for carrying out our study is only a partial sample of the international production in this field, and the scientific literature on SSRI is considerably wider, but the restrictions imposed by the data sources themselves (EMBASE: Psychiatry, in our case) condition the subsequent development of the material studied.

The scientific literature on SSRIs, as demonstrated with our studied material, has increased considerably in the past 2 decades, especially from 1988–1990 onward, a period that saw the clinical introduction of the majority of these agents in different countries of the world. Thus, it is in the 5-year period 1990–1994 in which the greatest increase in scientific production about these drugs occurred (372.99% up on the previous quinquennium). However, in the final years of the period analyzed this growth clearly slowed, with deceleration beginning in 1993 (largely owing to articles on fluoxetine) and a saturation point in 1997, which explains why our repertoire does not fulfil Price's law of exponential growth of scientific literature. Price already considered this phenomenon of saturation in his theory of the expansion of scientific literature [Price, 1963], and it seems normal when one analyzes, from a bibliometric perspective, the production of a family of drugs, because scientific research evolves toward the study of more novel agents as they appear in the therapeutic arsenal.

As we remarked earlier, introduction of SSRIs to the psychopharmacological therapeutic arsenal represented a considerable advance in the treatment of depression [De Vane, 1994; Muller and Volz, 1996; Johnson et al., 1997; López-Muñoz et al., 1998a]. However, in addition to depressive disorders, and following the DSM-IV criteria, the majority of anxiety disorders such as OCD, panic disorder, social phobia (social anxiety disorder), PTSD, and GAD, together with bulimia nervosa, have received the backing of the health authorities in different countries for their use, thanks to clinical trials documenting their efficacy [Vallejo, 1996; Sheehan and Harnett-Sheehan, 1996; Kerck and McElroy, 1997; Den Boer, 1998; Cuenca et al., 2002]. Nevertheless, over the past 2 decades, as reflected in the results of the present bibliometric study, numerous publications have appeared in the scientific literature demonstrating the utility of these drugs in a large number of disorders, both in the psychiatric ambit and in nonpsychiatric pathologies. Among the former we might mention substance abuse disorders, sexual disorders such as paraphilias, psychotic disorders, impulse-control disorders (trichotillomania, kleptomania, pathological gambling, and impulsive aggression), cognitive disorders such as dementia, childhood disorders (autism), borderline personality disorder, and other pathologies, such as anorexia nervosa, bipolar disorder, and pathological jealousy.

Evidently, the existence of such an ample bibliography and its growth must be correlated with the clinical use of these drugs. Numerous works have studied the

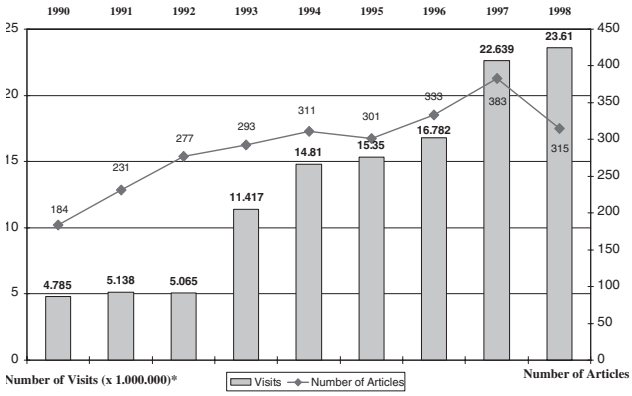

Figure 5. Relation between number of publications on SSRIs and evolution in the use of these drugs in the United States, during 1990–1998, per data submitted by Skaer et al. [2000]. *Data regarding the use of SSRIs in documented visits, from the U.S. National Ambulatory Medical Care Survey.

change in the pattern of consumption of antidepressants [Henry and Rivas, 1997; Ganguli et al., 1997; López-Ibor et al., 1999, 2000]. A recent study carried out in the United States [Skaer et al., 2000] supports increased use of antidepressants with data from everyday clinical practice. The authors carried out a retrospective analysis on antidepressant use between 1990 and 1998, according to documented visits, the use of SSRIs multiplied by 5, overtaking the use of TCAs from 1993. The final data of the study, corresponding to 1998, confirm the use of SSRIs in 57.7% of visits checked (40,925,824) and of TCAs in only 22.3%. Figure 5 shows this correlation between number of publications reported by us and data on use of SSRIs provided by Skaer et al. [2000]. Moreover, whereas the data of Skaer et al. [2000] confirm an increase of 45.9% in diagnoses of depression and of 90.6% in the use of antidepressants in patients diagnosed with depression, the use of antidepressants for any clinical reason increased by 125.4%, suggesting a high level of extra-antidepressant use. These data are confirmed in recent studies, such as the one by Loosbrock et al. [2002], which used National Disease and Therapeutic Index Physician Survey data from the United States and confidential questionnaires from 180 psychiatrists and 813 primary care physicians collected between 1997 and 1999, and found ICD-9-CM diagnostic categories between 19.7% and 26% of SSRIs prescriptions different from depressive disorders.

With regard to the pathologies most studied with each SSRI individually, there is a clear parallel with the effort necessary to prepare registration reports on each speciality in the indications in which they have been approved or in those at the stage of clinical development. Thus, although fluoxetine is the drug that contributes the greatest number of publications for almost all pathologies except panic disorder and social phobia, the relative importance of each pathology in relation to global production of each drug varies

considerably, with a notably greater relative participation of sertraline in PTSD and premenstrual syndrome, of paroxetine in GAD, social phobia, and depression, of fluvoxamine in OCD, of citalopram in panic disorder, and of fluoxetine only in bulimia nervosa. With regard to the unapproved pathologies, the pattern is equally variable. These results also seem to correlate with the standard of clinical use provided by Loosbrock et al. [2002], who confirmed that fluoxetine is the most proportionally SSRI used in eating disorders (1.4% of their prescriptions) and obesity (0.9%), paroxetine in anxiety disorders (12.6% of their prescriptions) and phobias (1.1%), citalopram in psychotic disorders (1.6% of their prescriptions), and sertraline in non-psychiatric disorders (2.2% of their prescriptions).

Relative to the journals most used in the diffusion of scientific literature on SSRIs, the first Bradford zone of our repertoire is composed by the *Journal of Clinical Psychiatry*, with 312 articles. Notwithstanding, 18.59% of them correspond to articles from supplements, and it is well known that these supplement articles are usually not original, but take part of issues sponsored by the pharmaceutical industry, over which the editor has no editorial control. If we exclude these articles from the repertoire, the journal furnishing more originals would be the *American Journal of Psychiatry* (282 articles).

Interesting data can also be extracted from the indices of transience and productivity of authors. That 57.79% of the articles are the responsibility of 27.88% of the authors (signatories to more than one work) indicates that scientific production on the SSRIs derives basically from a small number of research teams. This fact is confirmed even more if we take into account that 1.22% of authors, considered to be large producers (they sign at least 10 works), are responsible for 10.4% of the entire repertoire. Nevertheless, in our opinion, great productivity does not indicate scientific quality. In connection with this aspect, although only 10.38% of total production was directly generated in the pharmaceutical industry, it is obvious that these companies are behind a great part of the published investigation on SSRIs, through grants and other type of financial supports. However, it is difficult to quantify these subjects, and this issue is out of the direct objective of the present study.

Collaboration between authors, an indicator of the importance of teamwork, is reflected by the signatures/document index. Our data coincide with those of López-Piñero and Terrada [1992], who reported a collaboration index in the range 3.2–3.6 for scientific work in general published during the 1980s. In our analysis, the collaboration index doubles during the period studied, standing at 4.09 in the year 2000. In this regard, it appears undeniable a tendency exists toward an increase in the number of signatories of scientific work, owing largely to higher rates of collaboration between researchers. This is especially the case in the field of clinical pharmacology. This increase in scientific collaboration reflects not only interdepartmental support, which has become essential since the great diversification of study techniques and methodologies, but also a notable increase in collaboration between research groups from different countries. Great developments in clinical trials in recent decades have undoubtedly contributed to fomenting this collaborative phenomenon, especially those of a multicentre nature, that are more common in the area of psychopharmacology, with the aim of enrolling as quickly as possible the greatest possible number of subjects.

With regard to the PaI of the different countries in scientific production on the SSRIs, the databases normally used in this type of analysis, as in our case with EMBASE: Psychiatry, include in their Address of Authors section only the address of the first signatory or the person responsible for dealing with correspondence. Thus, the PaI of the different countries provided in this study will always be an approximation with regard to places in which research on SSRIs is generated—generally fairly accurate but not exact. Slight variations from reality are due to projects involving collaboration between research groups from different countries (multicenter and multinational clinical trials, etc.). The two main countries of the English-speaking world, the United States and the United Kingdom, head the ranking of producer countries and generate between them more than half the total scientific production (52.18%). That these two countries are home to the pharmaceutical companies responsible for development of the three most productive SSRIs agents (Eli Lilly, Beecham, and Pfizer) may explain, in part, this high PaI. In the same way, when the PaI is co-related with the health expenditure per capita of each country, we have observed a similar distribution (Fig. 4), which corroborates the fact that in general, the largest expenditure in health resources creates the greatest productivity in investigation. Nevertheless, when this analysis is carried out versus the total number of physicians in each country (as a sample of specialists more involved in the pharmacological investigation), we observed that the leaders are, successively, Denmark, New Zealand, the United Kingdom, Finland, and the Netherlands. The observed great difference in the case of Denmark is not surprising because the companies engaged in the preclinical and clinical development of two SSRIs (Lundbeck and Nordisk) are located in that country.

CONCLUSION

Despite the limitations inherent to bibliometric studies, thanks to our design, we are able to offer a picture of the representativeness and evolution of international research on the SSRIs. The results of the present study, together with the clinical studies on which they are based, show that the SSRIs are not solely antidepressant drugs. In fact, their efficacy in dealing with various anxiety disorders has converted

these drugs into the group of agents with the most promise as anxiolytics [Cuenca et al., 2002]. Moreover, the SSRIs have and will continue to have an ever-expanding range of clinical indications both within the psychiatric ambit and outside it [Alamo et al., 1998], to judge from promising results obtained for the different pathologies with which they have been studied. In consequence, scientific production in relation to these drugs will certainly continue to be abundant.

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