RESEARCH ARTICLE

A bibliometric analysis of scientific research on atypical antipsychotic drugs in India during 1998-2013

Francisco López-Muñoz[1,2,3], Venkatramanujan Srinivasan[4], Agustín Gutiérrez-Soriano[1], Winston W. Shen[5], Pilar García-García[2], Gabriel Rubio[3,6,7], Cecilio Álamo[2]

[1]*Faculty of Health Sciences, Camilo José Cela University, Madrid, Spain*
[2]*Department of Biomedical Sciences (Pharmacology Area), Faculty of Medicine and Health Sciences, University of Alcalá, Madrid, Spain*
[3]*Neuropsychopharmacology Unit, Hospital 12 de Octubre Research Institute (i+12), Madrid, Spain*
[4]*Sri Sathya Sai Medical Educational and Research Foundation, International Medical Sciences Research Study Center, Prasanthi Nilayam, Coimbatore, 641014,Tamilnadu, India*
[5]*Departments of Psychiatry, Wan Fang Medical Center and School of Medicine, Taipei Medical University, Taipei, Taiwan*
[6]*Department of Psychiatry, 12 de Octubre University Hospital, Madrid, Spain*
[7]*Department of Psychiatry, Complutense University, Madrid, Spain*

Correspondence: Francisco López-Muñoz
E-mail: flopez@ucjc.edu or francisco.lopez.munoz@gmail.com
Received: November 10, 2015
Published online: January 11, 2016

Background: We carried out a bibliometric study on the scientific publications on atypical antipsychotic drugs (AADs) from India. **Methods:** Using the EMBASE and MEDLINE databases, we performed the selection of documents produced in India. We applied bibliometric indicators of production and dispersion, namely Price's law on the increase of scientific literature and Bradford's law, respectively. We also calculated the participation index (PI) of different countries. The bibliometric data have also been correlated with relevant social and health data from India (including total per capita expenditure on health and gross domestic expenditure on research and development). **Results:** In this study, we identified 639 original documents published between 1998 and 2013 from India. Our results indicated fulfilment of Price's law (correlation coefficient r = 0.9619 after exponential adjustment *vs.* r = 0.9382 after linear adjustment). The most widely studied AADs were olanzapine (173 documents), clozapine (117), risperidone (100) and quetiapine (65). Publications appeared in 221 different journals, with only 4 of the top 10 journals having an impact factor greater than 2. Division into Bradford zones yielded a nucleus occupied by the *Indian Journal of Psychiatry* (53 articles). It is remarkable that the 27.38% of the production is devoted to "medical/pharmaceutical chemistry" field. India has the largest ratio PI AAD / PI Psychiatry and Neurology in the world's 12 most productive countries in biomedicine and health sciences. **Conclusions:** The publications on AADs in India have undergone exponential growth over the studied period, without evidence of reaching a saturation point.

Keywords: Atypical antipsychotics; Bibliometry; India; Schizophrenia

To cite this article: Francisco López-Muñoz, *et al*. A bibliometric analysis of scientific research on atypical antipsychotic drugs in India during 1998-2013. Mol Med Chem 2016; 2: e1113. doi: 10.14800/mmc.1113.

Introduction

Schizophrenia is a persistent, debilitating and severe mental illness, with an etiopathogenic base not totally known. According to epidemiological studies, its prevalence fluctuates between 0.5% and 1.0% of the population [1]. The World Health Organization (WHO) classifies this illness among the 10 disorders associated with greater disability in the adult population [2].

The main therapeutic pillar for schizophrenia over the last 60 years has 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 [3-5] and haloperidol [6]. These drugs dramatically influenced the management of patients with schizophrenia: they modified the course of psychosis made possible a new care organization, with a reduction in the number of patients admitted in health institutions and in days of hospitalization. Arguably, they enable better use and acceptance of psychotherapeutic measures for managing psychotic illnesses.

These first drugs, called first-generation, classical or typical antipsychotic drugs (AADs) [7], act essentially through blockage of dopamine D_2 receptors and are effectively in reducing the positive symptoms (hallucinations, delusion of schizophrenia). But their main limitation is their side effect burdens, principally extrapyramidal symptoms (EPS). Clozapine commercialized in the 1960s, later withdrawn in many countries because of its propensity to induce agranulocytosis [3], but reintroduced in the late 1980s, was a unique addition to the antipsychotic pantheon. This agent, apart from causing few EPS, shows efficacy for both positive and negative symptoms of schizophrenia, as well as in patients refractory to other antipsychotic drugs [8]. Clozapine has a complex pharmacological profile, especially at the level of the receptor blockage, and it opened the door to the AADs, with the introduction of risperidone in 1993.

The concept of atypicality of an antipsychotic drug has non-clinical and clinical criteria for atypicality [9]. Non-clinical criteria include efficacy in experimental approaches for evaluating antipsychotic drugs, without causing catalepsy, easily detected in laboratory animals. Atypical agents do not appear to induce up-regulation in the number of D_2 receptors or cause tolerance to the increase of dopamine turnover in chronic treatment to the same extent that typical agents do [10]. More recently, a series of biochemical criteria for atypicality has been discussed (greater 5-HT_{2A} than D_2 receptor antagonism, preferential localization for dopamine receptors in extra-striatal dopamine pathways, quick dissociation of the D_2 receptor, partial agonist activity on D_2 receptors, etc.). On the other hand, the clinical criteria for atypicality include antipsychotic efficacy at least similar to that of classical agents, together with a lower incidence of extrapyramidal effects. In some definitions, atypicality includes efficacy in treating refractory patients and against primary negative symptomatology, without having EPS and tardive dyskinesia of typical agents. A lower incidences of akathisia and hyperprolactinemia are also desirable criteria [10] but do not characterise all atypicals.

As shown in Table 1, the past 20 years has seen the introduction of a number of AADs (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, etc.). These agents have helped improve the quality of life of psychotic patients and have contributed to weakening the stigmatization that has traditionally accompanied schizophrenia [11]. The advent of these newer agents has been accompanied by a rise in the number of scientific publications pertaining to their pharmacology and clinical use. The current study assesses these trends in India.

India, the second most populated country of the world with over 1.2 billion people, is one of the fastest-growing major economies. Currently, it is the world's eleventh-largest economy by nominal gross domestic product (GDP), although the country ranks 140th in the world in nominal GDP per capita. The total expenditure on health as a percentage of DDP is 4.16% and the per capita government expenditure on health (PPP int. $) is $22.0 [12]. However, India is a country of contrasts, which population is predominantly rural, and where 36% of people still live below poverty line. It has been estimated that one in five people in India live with a mental illness (20 million), and there are four million people with schizophrenia [13]. People with mental disorders is an important barrier to mental health service utilization in India, due to the social importance of stigma and discrimination [14]. Moreover, in India people visit religious and traditional healers for general and mental health related problems.

Mental health expenditures by the government health department/ministry of India are 0.06% of the total health budget. There are currently around 3,500 practising psychiatrists in India, giving a psychiatrist-to-population ratio of 0.301/100,000, which is very low compared with other developed countries like the USA (13.7/100,000). Most of the psychiatrists are based in cities or private hospitals. Modern psychiatry in India is a relatively recent introduction with subsequent development of psychiatric practices. National Mental Health Programme (NMHP) has been implemented since 1982, and intends to attend to the mental health needs of all her citizens [15]. As an example of this development, there was an eight-fold increase in budget for

Table 1. Clinical development of atypical antipsychotic drugs

	Company	Launch	
Clozapine	Wander Laboratories	1972 [a]	Switzerland
Zotepine	Fujisawa	1982 [b]	Japan
Amisulpride	Synthelabo	1986	Portugal
Risperidone	Johnson & Johnson	1993	UK / Canada
Sertindole	Abbott Laboratories	1996 [c]	UK
Olanzapine	Eli Lilly	1996	USA / UK
Quetiapine	AstraZeneca	1997	USA / UK
Ziprasidone	Pfizer	2001	USA
Perospirone	Dainippon Sumitomo Pharma	2001	Japan
Aripiprazole	Otsuka / Bristol-Myers Squibb	2002	USA
Paliperidone	Janssen Pharmaceutica	2007	USA
Blonanserin	Dainippon Sumitomo Pharma	2008	Japan
Asenapine	Schering-Plough	2009	USA
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.

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

Zones	Number of journals	Number of articles	Bradford's constants
1	1	53	
2	2	56	2
3	4	57	2
4	6	57	1.5
5	7	50	1.16
6	8	51	1.14
7	11	53	1.37
8	16	53	1.45
9	24	53	1.5
10	39	53	1.62
11	53	53	1.35
12	50	50	---

Total number of journals = 221; Total number of articles = 639; Average number of articles = 53.25; Average number of articles, excluding the last Bradford zone = 53.54

Table 3. The 10 journals with highest number of publications on atypical antipsychotic drugs

Journal	No. Documents	PI	IF [a]
Indian Journal of Psychiatry	53	8.29	---
Journal of Neuropsychiatry and Clinical Neurosciences	29	4.53	2.397
Indian Journal of Pharmacology	27	4.22	0.583
Australian and New Zealand Journal of Psychiatry	21	3.28	3.293
Journal of Clinical Psychiatry	14	2.19	5.812
International Journal of Pharmacy and Pharmaceutical Sciences	12	1.87	---
General Hospital Psychiatry	10	1.56	2.977
Indian Journal of Medical Sciences	10	1.56	---
International Research Journal of Pharmacy	10	1.56	---
Journal of Chemical and Pharmaceutical Research	10	1.56	---

PI, participation index; IF, impact factor 2012. [a] Journal Citation Report, 2013 (JCR, 2013).

the Tenth Five-Year Plan (2002-2007). In this sense, and in relation to the topic of our study, the proportion of prescriptions for atypical medications in India has increased markedly during the last years [16-18].

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 [19]. Despite their methodological limitations, bibliometric studies are useful tools for assessing the social and scientific relevance of a given discipline or field [20]. Our group has studied, using 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 [21-25]. Recently, we have analysed the evolution of the scientific literature on AADs made in different countries of Asia-Pacific region

Table 4. Distribution of papers on atypical antipsychotic drugs in the world's 12 most productive countries in biomedicine and health sciences for the period 1998-2013

	Country *	% *	Psy-Neurol ** (%)	AADs (%)	AADs/Psy-Neurol
1	USA	26.81	35.14	32.23	1.05
2	UK	7.61	9.82	6.98	0.81
3	Germany	6.52	8.08	6.24	0.88
4	Japan	6.22	6.36	4.29	0.77
5	China	5.55	4.07	2.80	0.79
6	France	4.41	4.73	2.94	0.71
7	Italy	4.09	4.81	4.86	1.14
8	Canada	3.91	4.90	5.35	1.18
9	Spain	2.96	3.07	4.01	1.50
10	Australia	2.79	3.36	2.80	0.95
11	Netherlands	2.52	3.15	2.60	0.95
12	India	2.45	1.70	3.52	2.37

Psy-Neurol (area of focus in Neurology and Psychiatry); AADs (atypical antipsychotic drugs). * The world's 12 most productive countries in biomedicine and health sciences for the period 1998-2013, ** Their productivity in the discipline of Psychiatry and Neurology. Total documents 1998-2013: 13,523,258. Total documents in the Neurology and Psychiatry area 1998-2013: 1,594,827. Total documents on AADs 1998-2013: 18,353.

Table 5. Contribution of different institutions in India

Centre	*n*
National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore	48
Central Institute of Psychiatry, Ranchi	44
Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarth	37
G.B. Pant Hospital, New Delhi	21
Panjab University, Chandigarh	15
Kasturba Medical College, Manipal University, Karnataka	15
Banaras Hindu University, Varanasi, Uttar Pradesh	11
All India Institute of Medical Sciences (AIIMS), New Delhi	10
Dr. Reddy's Laboratories Ltd., Hyderabad	10
Indira Gandhi Medical College, Shimla, Himachal Pradesh	10
JSS College of Pharmacy, Mysore	10

n (number of documents of database)

[26-31]. In this study reported here, we applied the same method to investigate trends in AAD publications in India.

Methods

Data collection

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: both participate in EMBASE Biomedical Answer web (Elsevier B.V., The Netherlands).

Using remote downloading techniques, we chose documents containing, in the author address (AD) section the descriptor India, and in the title (TI) 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, confining the year of publication to the period 1998-2013. 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, reviews, editorials and letters-to-the editor. All duplicated documents were eliminated: 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 relevant papers into five groups: "experimental pharmacology," "medical/pharmaceutical chemistry," "clinical efficacy," "tolerance and/or safety," and "not specified" grouping.

Bibliometric indicators

Among the bibliometric indicators Price's law is without doubt the indicator most widely used in analysis of the productivity of a specific discipline or a particular country, reflecting a fundamental aspect of scientific production, namely exponential growth [32]. To assess whether the growth of scientific production in AADs follows Price's law of exponential growth, we made a linear adjustments to the data obtained, according to the equation y = 7.6132x - 24.775;

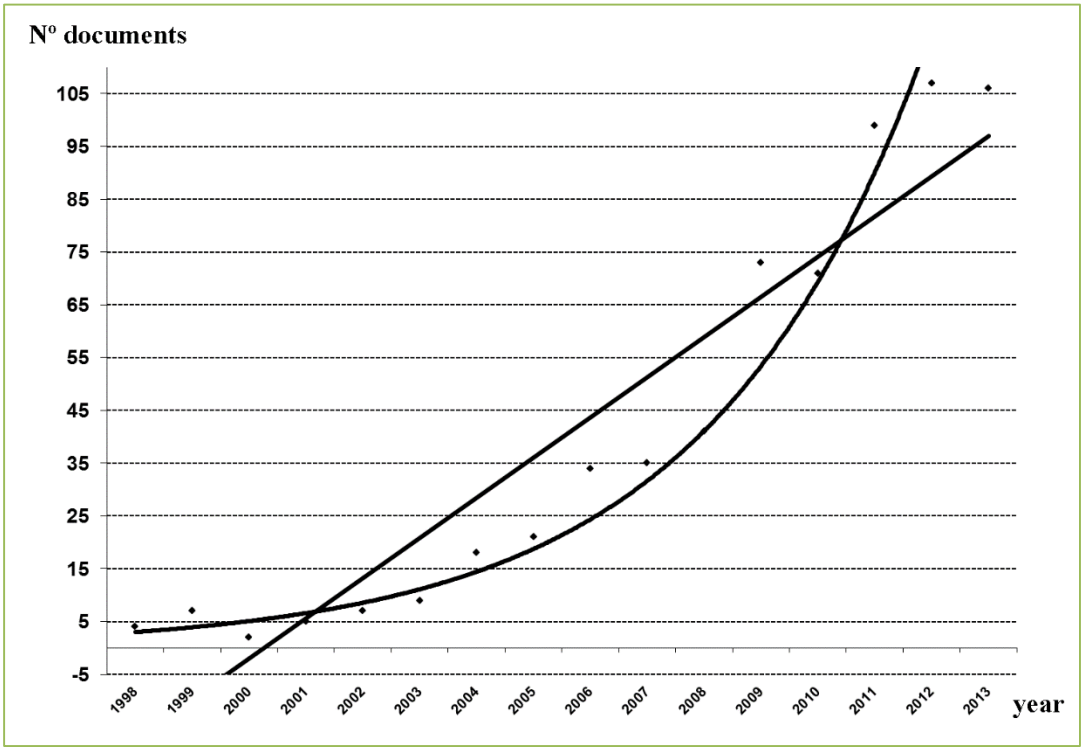

Figure 1. Growth of scientific production on atypical antipsychotic drugs in India. A linear adjustment of the data was carried out, and a fitting to an exponential curve, in order to check whether production follows Price's law of exponential growth. Linear adjustment: $y = 7.6132x - 24.775$ ($r^2 = 0.8803$). Exponential adjustment: $y = 2.31e^{0.2616x}$ ($r^2 = 0.9253$).

and a further adjustment to an exponential curve, according to the equation $y = 2.313e^{0.2616x}$.

We also applied Bradford's law as an indicator of the dispersion of scientific information. 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 [33]. Thus, each zone would contain a similar number of documents, 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.

As an indicator of the publications' repercussion we used the impact factor (IF). 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 the journal is cited in the source journals of the SCI during the two previous years and the total number of articles published by that journal in those two years. The JCR lists scientific journals by specific areas, ascribing to each of them their corresponding IF and establishing a ranking of "prestige" [34]. In this study, we used the IF data of 2012 published in the JCR of 2013.

Another indicator included in the present analysis was the national participation index (PI) of India for overall scientific production (the ratio of the number of documents generated by India and the total number of documents on a particular topic). This PI has also been compared with global PI in biomedical and health sciences (as well as for psychiatry and neurology areas in particular). Likewise, the PI has been correlated with some economic and health data, such as GDP per capita, total per capita expenditure on health and proportional gross domestic expenditure on research and development (R&D). The PI has also been correlated with the corresponding PI for the world's 12 most productive countries during the period 1998-2013. The PI health data were obtained from the Organisation of Economic Co-operation and Development (OECD) Health Division [35] and WHO Department of Health Statistics and Informatics [12].

Results

After study of the database analysed during the period 1998-2013, we obtained 639 original documents (articles, reviews, editorials and letters-to-the editor) dealing with

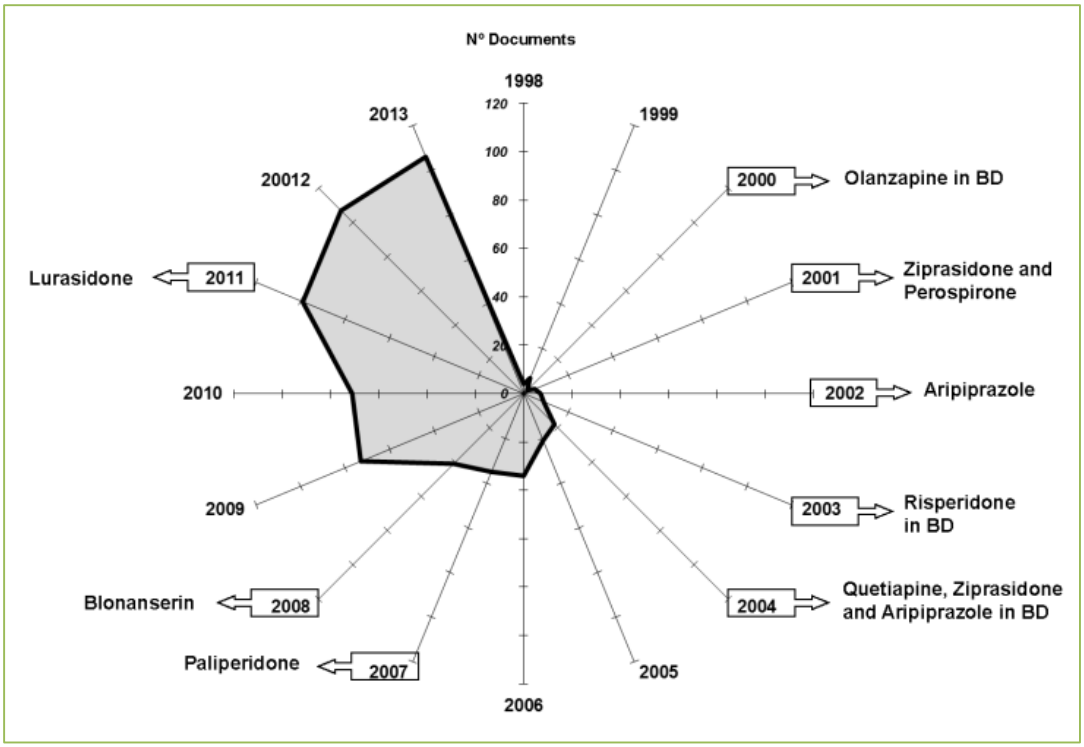

Figure 2. Number of documents on atypical antipsychotic drugs (1998-2013) and international authorization of different drugs.

different aspects related to AADs in India. Of these, 173 related to olanzapine, 117 to clozapine, 100 to risperidone, 65 to quetiapine, 58 to aripiprazole, 41 to amisulpride, 37 to ziprasidone, 15 to paliperidone, 9 to asenapine, 7 to iloperidone, 3 to blonanserin, 2 to zotepine and 1 to lurasidone. No document relative to sertindole or perospirone was found.

As shown in Figure 1, over the last 16 years there has been a marked increase in the number of publications generated in relation to AADs in India. The mathematical adjustment to an exponential curve in Figure 1, permitted us to calculate a correlation coefficient r = 0.9619, indicating 7.47% of variance unexplained by this fitting. In contrast, the linear adjustment of the measured values provides an r = 0.9382, with a portion of unexplained variance of 17.14%. With these data we can conclude that the database analyzed was more in keeping with an exponential fitting than a linear one, and that the postulates of Price's law were fulfilled.

As indicated in Figure 2, the clinical introduction of the new AADs in different countries of the world, together with their licensing for treating bipolar disorder, appears to have contributed substantially to the increase in scientific production in the field of AADs in India. Figure 3 shows the evolution that had occurred in the last sixteen years of all AAD literature. Since 2007, the growth was mainly due to publications on olanzapine and clozapine.

Applications of Bradford's model showed the mean number of articles per Bradford zone to be 53.25. Table 2 shows the division into Bradford's areas of the material under study. The nucleus or first zone is made up exclusively of the *Indian Journal of Psychiatry*, with 53 articles, and the second zone include 2 journals (*Journal of Neuropsychiatry and Clinical Neurosciences* and *Indian Journal of Pharmacology*). The rest of the journals analysed were included in zones 3 to 12. A total of 221 different journals published material pertinent to this article, but it was notable that the 10 most used journals accounted for 30.67% of all there publications. Table 3 lists these 10 journals their corresponding IFs according to the JCR of 2012 and the PI of the journals on the total database in the analysed period. It will be noted that those journals most extensively used for the diffusion of AAD works half lack IFs and only 4 of them has an IF greater than 2.

Manually classifying articles, we found that 37.24% addressed "tolerance and safety," 14.55% "clinical efficacy," 17.37% "experimental pharmacology", 27.38% "medical/pharmaceutical chemistry" and 3.46% "others / not specified" (mainly articles of prescribing patterns and drug reviews). Using disease classification, we found that clinical studies were mainly devoted to schizophrenia (n = 46) and bipolar disorder (n = 12).

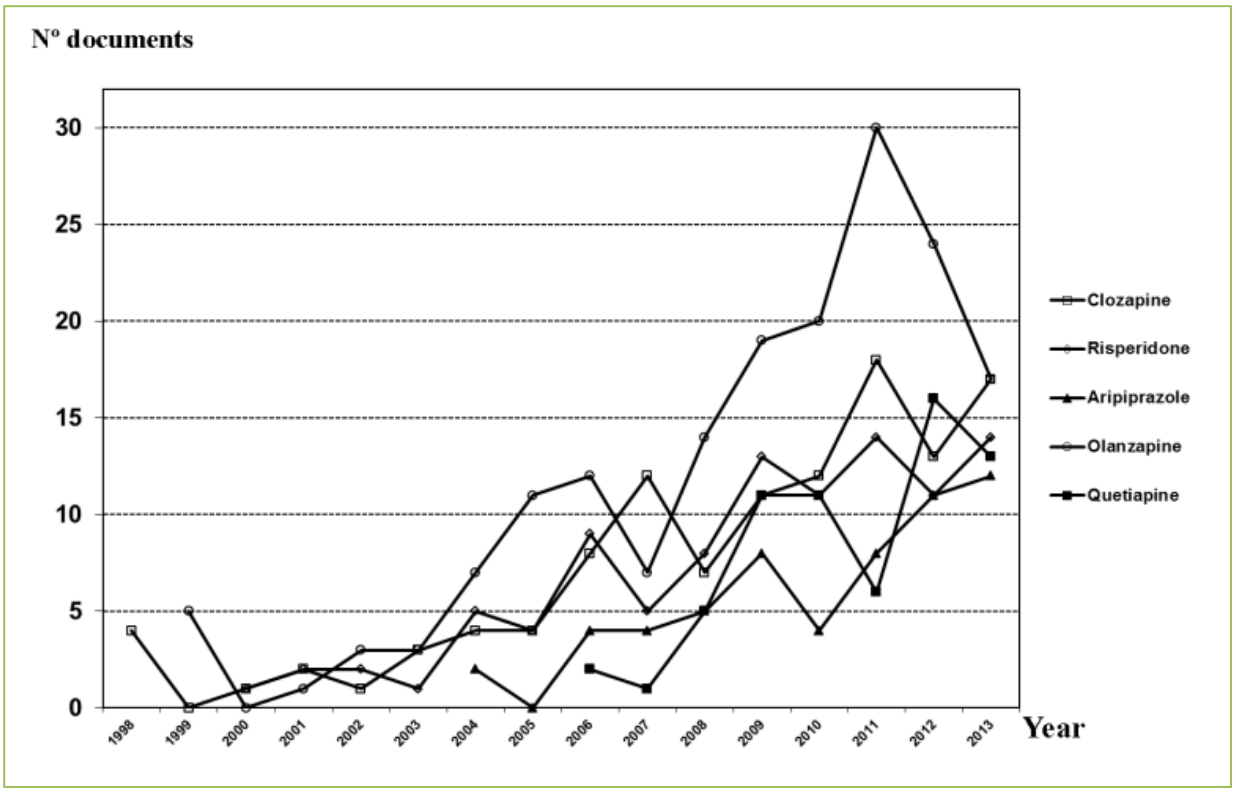

Figure 3. **Evolution of documents on 5 more relevant atypical antipsychotic drugs (MEDLINE and EMBASE: 1998-2013).**

As shown in Table 4, the general contribution of Indian science within this thematic area, had a global PI of 3.52 with respect to world production over the period under study. Among the countries generating AAD research, the most prominent is the USA (PI is 32.23), followed by the UK (PI = 6.98), Germany (PI = 6.24), Canada (PI = 5.35) and Italy (PI = 4.86). But if we consider the productivity of these countries specifically in the fields of psychiatry and neurology, only 4 countries of the 12 largest producers in biomedicine and health sciences (in the period 1998-2013) devoted a higher percentage of attention to the AAD studies (India, Spain, Canada and Italy) (Figure 4).

As far as social-health parameters, Figure 5 shows the correlation between PI on AADs and the GDP per capita of the highest scientific producers in health sciences. Analysing the correlation between PI and the per capita health expenditure of each of these countries (Figure 6), we found that the distribution was quite similar, apart from India and China, although in these cases it is an artefact due to the small Indian and Chinese per capita health expenditure (141, and 432 PPP Int $, respectively). However, it is striking the low ratio of countries like Netherlands, France and Australia.

Table 5 shows the most productive institutions in relation to the material under study. We defined the corresponding institution solely based on the information provided in the AD field in the EMBASE Biomedical Answer web database. The top three rankings are National Institute of Mental Health and Neurosciences (NIMHANS) of Bangalore, Central Institute of Psychiatry of Ranchi, and Postgraduate Institute of Medical Education and Research (PGIMER) of Chandigarth. The three institutions have generated 20.18% of the papers that make up the sample.

Discussion

Bibliometric studies constitute useful tools for assessing the social and scientific importance of a given discipline over a specific time period. The term "bibliometrics" was introduced by Pritchard in 1969, to define the application of mathematical and statistical methods to the process of dissemination of written communication in the area of scientific disciplines, using quantitative analysis of the different aspects of this type of communication [36]. These analyses give an overview of the growth, size 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 [19]. The design of the present analysis permitted a global assessment on the growth of scientific publications on ADD in India since 1998.

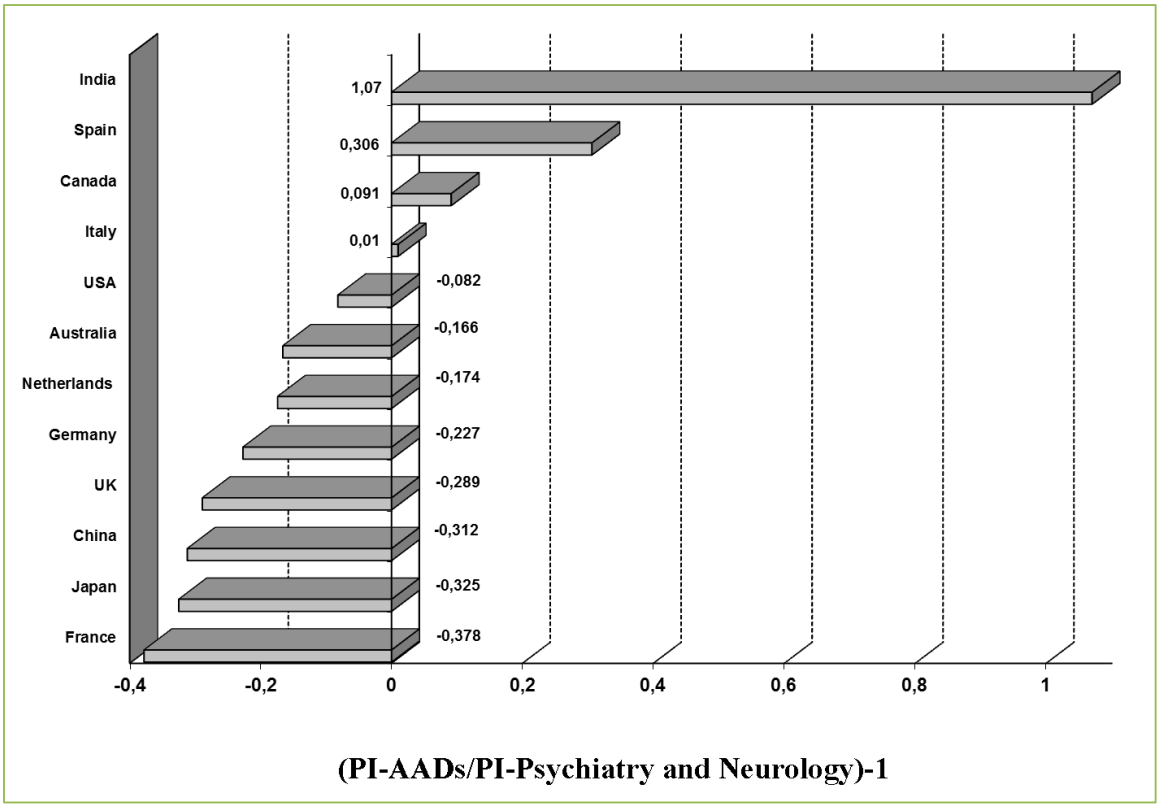

Figure 4. Relationship between production of scientific literature on atypical antipsychotic drugs (AADs) and total production in the field of psychiatry and neurology in the world's 12 most productive countries in biomedicine and health sciences. PI, participation index; AADs, atypical antipsychotic drugs.

The number of scientific papers has increased substantially in recent years in India. This growth is exponential, with the correlation coefficient r = 0.9619 after exponential adjustment *vs.* r = 0.9382 after linear adjustment. This finding is concordant with the results of our earlier studies from other countries of Asia including Taiwan [26], Japan [27], and South Korea [28], where exponential growths in AAD publications have occurred. These bibliometric data also show a close correlation with the prescription data in these countries. Database of the Research on Asian Psychotropic Prescription Patterns (REAP) study (2001-2009) show an increase of the use of AADs in eight Asian countries and territories including China, Hong Kong SAR, India, Japan, Korea, Malaysia, Singapore, and Taiwan [37]. It is also confirmed this evolution in specific studies on psychotropic drugs use pattern in India [16-18]. Grover *et al*., [38] in a study conducted in India, have confirmed that the most commonly prescribed antipsychotic medication is olanzapine (20.7% of patients with an organic mental disorder, 40.8% with psychotic disorder, 30.2% with bipolar disorder); quetiapine and risperidone were the other commonly prescribed antipsychotics.

The greatest increase in the AAD scientific literature coincides with its approval for marketing by the Food and Drug Administration in the USA (FDA) and other international regulatory agencies in the treatment bipolar disorder. Since 2004, other AADs such as risperidone, quetiapine, ziprasidone, aripiprazole and asenapine have been also approved for treating manic episodes, and olanzapine and aripiprazole for relapse prevention in patients with bipolar disorder [39]. Quetiapine is indicated as monotherapy for the acute treatment of depressive episodes associated with bipolar disorder, and olanzapine-fluoxetine combination for treating treatment-resistant major depressive disorder. Also aripiprazole was approved in 2007 by the FDA for treating treatment-resistant major depression as an add-on to an antidepressant [39]. Finally, AADs are also commonly used (and studied) in many off-label indications, such as toxic psychosis, agitation symptoms, tics, substance abuse disorders and anxiety disorders [40, 41]. In the analysis of individual AADs, olanzapine was found to be the agent most widely studied in India (Figure 3).

In the current study, we also applied indicators of impact and excellence of the publications. The fact that such prestigious journals as the *Journal of Clinical Psychiatry* (IF = 5.812) or *Australian and New Zealand Journal of Psychiatry* (IF = 3.296) published articles on AADs from India is an important factor in this regard, indicating the

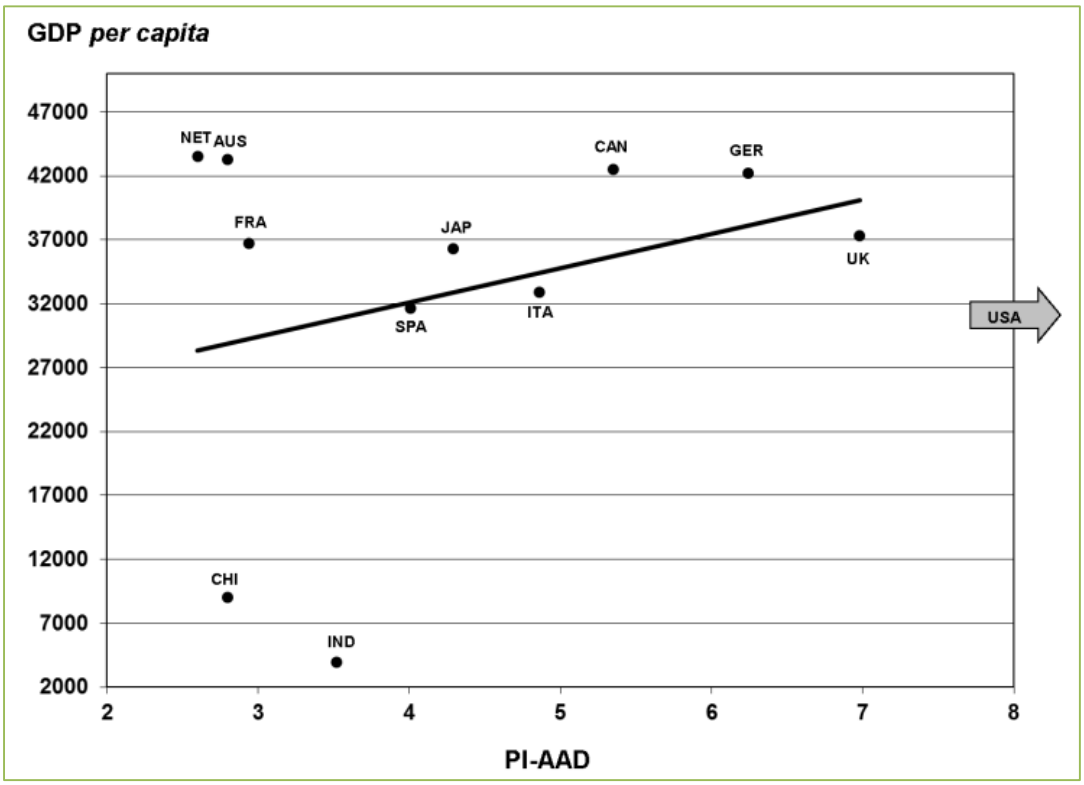

Figure 5. Relationship between production of scientific literature on AADs and *per capita* gross domestic product in the world's 12 most productive countries in biomedicine and health sciences. We have excluded the United States from the graph in order to give a clearer reflection of the rest of the countries. GDP (Gross Domestic Product), PI (Participation Index), AADs (atypical antipsychotic drugs). The economic data were obtained from the website of the World Health Organization (http://www.who.int/country/es/) (WHO, 2013). Economic data are expressed in international dollars (data 2012).

projection (both clinical and social) that this country has acquired in recent years. However, the fact that 5 of the top ranking journals lack IF shows that the scientific quality of publications from India should continue to improve. This also happens in the other Indian scientific research, where differences have been described with other developed and developing countries [42], even in the specific field of schizophrenia [13]. It also highlights the extensive use of domestic journals by Indian researchers. In fact, of the 10 top ranking, 6 of them correspond to journals whose head office is based in India. The articles published in these 6 journals account for 19.09% of total production on AADs. However, this also speaks of the great development that is experiencing the scientific and medical publishing industry in this country.

In our repertoire, the ratio of papers on "medical/pharmaceutical chemistry" is very high (27.38%) and far higher than in other countries in the Asia-Pacific region [26-31]. Gupta *et al* [43] have confirmed the enormous growth of publications of India in biochemistry, genetics and molecular biology area, which was found to be 11.18% (70,955 publications) during 1996-2011, which increased from 10.44% (19,859 papers) during 1996-2003 to 11.50% (51,096 papers) during 2004-2011. The world publication share of India in biochemistry, genetics and molecular biology area was 2.52% during 1996-2011 and increased from 1.65% during 1996-2003 to 3.18% during 2004-2011. The average citation per paper registered by all Indian publications in this area was 9.11 during 1996-2011, which decreased from 15.27 during 1996-2003 to 5.56 during 2004-2011 [43]. Moreover, analyzing the quality and citation impact of schizophrenia research in India under different subjects, it was found that chemistry had scored the highest impact (10.70 citations per paper) [13]. During the period 1996-2011 Indian papers in clinical biochemistry were 5,049 with 7.12% of share of the total publications in this area; molecular biology papers were 8,120 with 11.42% of share. Publications on drug discovery constituted 6,442 papers that accounted for 21.88% of the publication input in pharmacology, toxicology and pharmaceutics during 1996-2011 period. Among developing countries the fastest annual average growth rate achieved by India was 10.42% compared to China which achieved 19-65% growth rate [43].

The great increase in publications in the field of medicinal biochemistry, genetics and molecular biology is attributed to

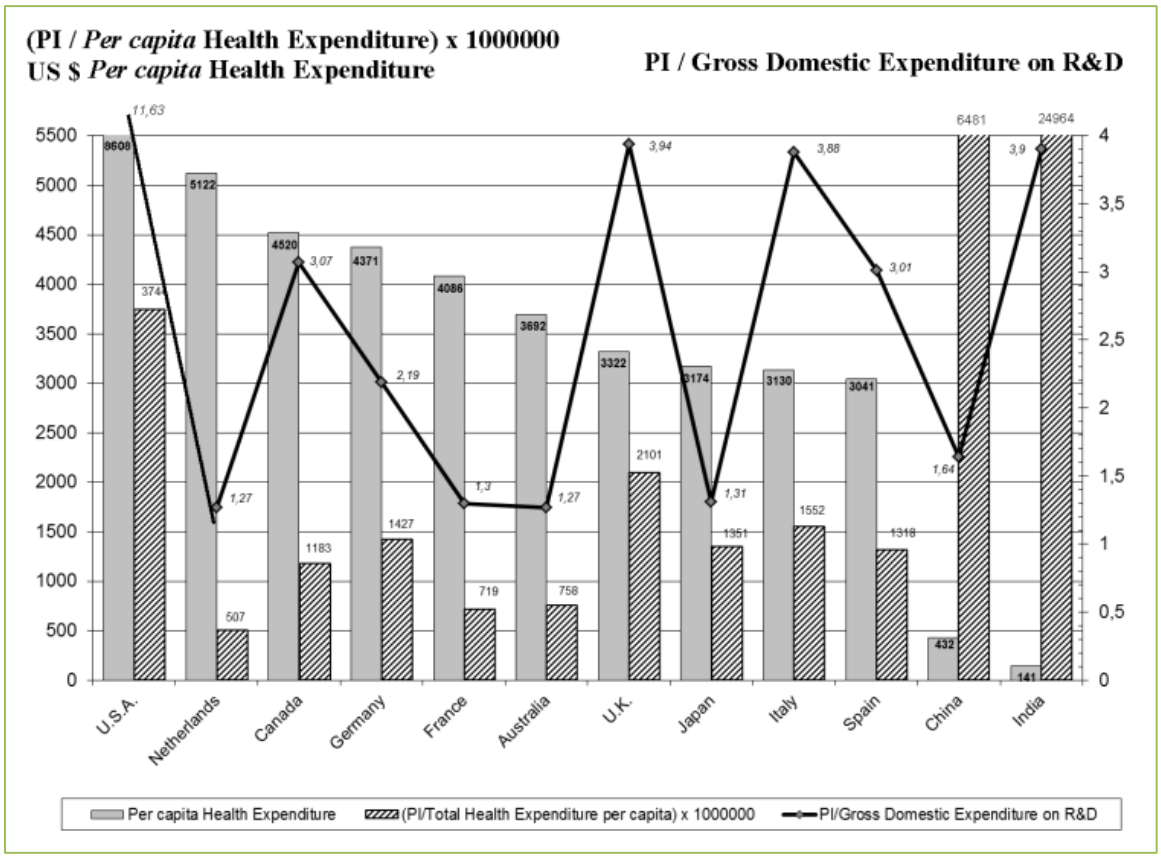

Figure 6: **Per capita Health Expenditure and relationship between production of scientific literature on atypical antipsychotic drugs and per capita health expenditure and gross domestic expenditure on research and development, in the world's 12 most productive countries in biomedicine and health sciences.** PI, participation index. Total Health Expenditure per capita PPP Int $ (data WHO 2013) (http://www.who.int/country/es/).Gross Domestic Expenditure on research and development (%). Data OECD 2013, except Australia and Japan (data 2010) and China (data 2009) (http://www.oecd-ilibrary.org/science-and-technology/gross-domestic-expenditure-on-r- d_2075843x- table1).

increase in the number of universities and research institutions in India during the period from 1950 to 2011 [43]. However, in the field of schizophrenia, scientific productivity in India is concentrated in a small number of institutions, according to Gupta and Bala [13]: the three first institutions of ranking generated 36.84% of the papers on this topic in the period 2002-11. Our results confirm that these three institutions (see Table 5) were also the most productive on AADs (20.18% of the documents of our sample).

According to Gupta *et al.* [43], the developed and developing countries differ significantly in their annual Science and Technology publication growth rate. The annual publication data during 1996-2011 was 1.75% to 12.74% for developed countries and 9.69% to 19-65% for developing countries. This shows that not only India but most of the developing countries like China, South Korea, Brazil, Taiwan shown significant increase in the publication rate. India ranks 10th among the top 20 productive countries in Science and Technology with its global publication share of 2.29% when computed from cumulative world publication rate [42]. These data are similar to those obtained by us in the period analyzed (1998-2013).

Our study results confirm that during the period 1998-2013, papers in the area of psychiatry and neurology accounted for 8.19% of the total scientific production in India. As we have shown in recent studies, scientific research on antipsychotic drugs is one of the fastest growing fields within the field of psychiatry in Asia [26-31]. Also, by applying bibliometric tools, other authors have reported the research activity in the field of schizophrenia as greater to that in other fields of psychiatry [44]. These authors reported that the number of references on schizophrenia in MEDLINE has followed the general increase of medical publications, accounting for 0.42% compared to the total medical literature in the period studied of 1993-2011. In the specific field of schizophrenia, India shows an annual average publication growth rate of 21.80% during 2002-11 (global publications

share increased from 0.83% to 2.33% from the year 2002 to the year 2011) [13].

Two major English-speaking countries, the USA and the UK, head the ranking of AAD paper-producing countries, and between them generate more than a third of total AAD scientific production in this field (39.21%). Of course, both of countries are popular in population; therefore, they have more patients to receive ADDs and more psychiatrists to publish ADD papers. The fact that in these two countries are home to the pharmaceutical companies responsible for the AAD development (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), may further help explain this high PI. At this point, it is interesting to note that the pharmaceutical industry in India is among the significant emerging markets for global pharma industry. The Indian pharmaceutical market is expected to reach $48.5 billion by 2020, and is among the top 12 Biotech destinations of the world. Currently, the pharmaceutical industry in India is the world's third-largest in terms of volume, primarily driven by a large population, evolving patient demographics, increasing health care expenditure, growing urbanisation, rising life expectancy, and active private-sector participation [45]. In the last 10 years, the Government of India has adopted strategies to boost the country's healthcare industry. Moreover, the Government of India is providing incentives to encourage investment in the pharma sector.

Table 4 shows the data from the 12 most productive countries in biomedicine and health sciences and compares the data for general productivity in the psychiatry and neurology disciplines, with productivity in the specific field of AADs. Our results are similar to those reported by Gupta and Bala [13]; according to this study, India holds 12th rank among the productive countries in medicine research consisting of 65,745 papers with a global publication share of 1.59% [46].

It is worth nothing that countries such as India, Spain and Canada sit near the top of the ranking for producing publications on AADs (see also Figure 4). Other countries, such as the Italy and USA, maintain rates of AAD publication productivity that are in proportion with their global index for psychiatry. On the other side of the scale, it is interesting to note the lower relative interest in these drugs, within the context of their general production in psychiatry, in countries such as China, Japan and France.

As far as social-health parameters are concerned, if we correlate the scientific documents contributed by the principal producers of AADs literature with their GDP per capita, we observe a homogeneous distribution for a large group of them (France, Japan, Spain, Italy, Germany, United Kingdom and Canada). However, there is less interest in this topic, in relation to their economic potential, in countries such as Netherlands and Australia (Figure 5). Dispersion of India and China is due to its low GDP per capita. Figure 6 shows that the higher the spending on health, the greater the research production, across countries. Particular, country's scientific production in a given field tends to reflect a science research and development begun some years before the period analysed [23, 24]. However, the low ratios of countries such as Australia, France or Netherlands, is striking. The correlation analysis between scientific AAD production and the GDE on research and development show also Australia, France or Netherlands at the last three positions.

Limitations of the study

Previous bibliometric studies have addressed limitations characteristic of this sociometric approach [47]. Regarding this particular paper, there are some main limitations. First, we might have excluded some papers on AADs if the authors did not put our study inclusion descriptors in the titles or as key words. Moreover, local journals that are not indexed in MEDLINE and Excerpta Medica during the study period, and those contributions from Indian investigators at scientific conferences and meetings were also not included in our study. Second, in the AD section using the descriptor "India," we included those papers with authors specifying "India" in their addresses only. We did not count those papers as Indian papers if the corresponding authors of the articles from India had not put their Indian addresses. Third, the use of the SCI impact factor to determine the merit or quality of scientific contributions is debatable. The citation count applied in calculating the impact factor may not directly reflect the importance or quality of one study; on the contrary, it may only represent the topic of a given study being "more fashionable", or even "not yet mature" and/or "in need of more studies." There are suggestions that universities should not mainly use the measurement of impact factor to evaluate the academic outputs of their faculty members [48, 49].

Conclusions

This study offers an objective picture of the representativeness and evolution of international research on AADs in India, and addressed the parameters of quality and dissemination most commonly used at an international level. The data obtained confirm, as also indicate Gupta and Bala [13], which schizophrenia should be considered as a priority area in the current and future national Science and Technology plans of India. However, research in this field

will continue to grow in the coming years because (1) the ideal antipsychotic drug has not yet been found [11], and (2) the list of clinical use of those versatile ADD drugs have been ever-increasing [50].

Conflicts of interest

The authors have no proprietary or commercial interest in any materials discussed in this article and no conflicts of interest exist.

References

1. Goldner EM, Hsu L, Waraich P, Somers JM. Prevalence and incidence studies of schizophrenia disorder: a systematic review of literature. Can J Psychiatry 2002; 47:833-843.
2. World Health Organization. Mental health: new understanding, new hope. Geneva: WHO; 2001.
3. Shen WW. A history of antipsychotic drug development. Compr Psychiatry 1999; 40:407-414.
4. López-Muñoz F, Alamo C, Rubio G, Cuenca E. Half a century since the clinical introduction of chlorpromazine and the birth of modern psychopharmacology. Progr Neuro-Psychopharmacol Biol Psychiatry 2004; 28:205-208.
5. López-Muñoz F, Alamo C, Cuenca E, Shen WW, Clervoy P, Rubio G. History of the discovery and clinical introduction of chlorpromazine. Ann Clin Psychiatry 2005; 17:113-135.
6. López-Muñoz F, Álamo C. The consolidation of neuroleptic therapy: Janssen, the discovery of haloperidol and its introduction into clinical practice. Brain Res Bull 2009; 79:130-141.
7. Hippius H. A historical perspective of clozapine. J Clin Psychiatry 1999; 60 (Suppl. 12):22-23.
8. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. Arch Gen Psychiatry 1988; 45:780-796.
9. Meltzer HY. What's atypical about atypical antipsychotic drugs? Curr Opin Pharmacol 2004; 4:53-57.
10. Álamo C, Cuenca E, López-Muñoz F, García-García P. Neurolépticos y Antipsicóticos. Aspectos farmacológicos de la evolución del tratamiento de la esquizofrenia. In Nuevas Generaciones en Neurociencias. Las Esquizofrenias. Sus hechos y valores clínicos y terapéuticos. Edited by Chinchilla A. Barcelona: Elsevier Masson; 2007: 343-401.
11. López-Muñoz F, Álamo C, Neurobiological background for the development of new drugs in schizophrenia. Clin Neuropharmacol 2011; 34:111-126.
12. World Health Organization Department of Health Statistics and Informatics. World Health Statistics 2013 (May, 2013). Geneva: WHO; 2013.
13. Gupta BM, Bala A. A scientometrics approach to schizophrenia research in India: An analysis of publications output during 2002-11. Asian J Psychiatry 2013; 6:292-298.
14. Shidhaye R, Kermode M. Stigma and discrimination as a barrier to mental health service utilization in India. Int Health 2013; 5:6-8.
15. Das A. The context of formulation of India's mental health program: Implications for Global Mental Health. Asian J Psychiatry 2014; 7:10-14.
16. Shrivastava A, Johnston M, Terpstra K, Stitt L, Shah N. Atypical antipsychotics usage in long-term follow-up of first episode schizophrenia. Indian J Psychiatry 2012; 54:248-252.
17. Vaithiyam A. A study of an antipsychotic prescription pattern of patients with schizophrenia in a developing country. Eur Psychiatry 2012; 27 (Suppl. 1).
18. Sarkar P, Chakraborty K, Misra A, Shukla R, Swain SP. Pattern of psychotropic prescription in a tertiary care center: A critical analysis. Indian J Pharmacol 2013; 45:270-273.
19. Bordons M, Zulueta MA. Evaluación de la actividad científica a través de indicadores bibliométricos. Rev Esp Cardiol 1999; 52:790-800.
20. White HD, McCain KW. Bibliometric. Ann Rev Inf Sci Technol 1989; 24: 119-186.
21. López-Muñoz F, Marín F, Boya J. Evaluación bibliométrica de la producción científica española en neurociencia. Análisis de las publicaciones de difusión internacional durante el periodo 1984-1993. Rev Neurol 1996; 24:417-426.
22. López-Muñoz F, Alamo C, Rubio G, García-García P, Martín-Agueda B, Cuenca E. Bibliometric analysis of biomedical publications on SSRIs during the period 1980-2000. Depres Anxiety 2003; 18:95-103.
23. López-Muñoz F, Vieta E, Rubio G, García-García P, Alamo C. Bipolar disorder as an emerging pathology in the scientific literature: a bibliometric approach. J Affect Dis 2006; 92:161-170.
24. López-Muñoz F, Álamo C, Quintero-Gutiérrez FJ, García-García P. A bibliometric study of international scientific productivity in attention-deficit hyperactivity disorder covering the period 1980-2005. Eur Child Adolesc Psychiatry 2008; 17:381-391.
25. López-Muñoz F, García-García P, Sáiz-Ruiz J, Mezzich JE, Rubio G, Vieta E, *et al*. A bibliometric study of the use of the classification and diagnostic systems in psychiatry over the last 25 years. Psychopathology 2008; 41:214-225.
26. López-Muñoz F, Shen WW, Moreno R, Molina JD, Noriega C, Pérez-Nieto MA, *et al*: International scientific productivity on second-generation antipsychotic drugs in Taiwan: a bibliometric study. Taiwanese J Psychiatry 2012; 26:114-129.
27. López-Muñoz F, Shinfuku N, Shen WW, Moreno R, Molina JD, Rubio G, *et al*. Thirty years of scientific research on second-generation antipsychotic drugs in Japan: A bibliometric analysis. Open J Psychiatry 2013; 3:18-25.
28. López-Muñoz F, Shen WW, Pae CU, Moreno R, Rubio G, Molina JD, *et al*. Trends in scientific literature on atypical antipsychotics in South Korea: A bibliometric study. Psychiatry Invest 2013; 10:8-16.
29. López-Muñoz F, Chung AK, Shen WW, Huelves L, Noriega C, Rubio G, *et al*. A bibliometric study of scientific research on second-generation antipsychotic drugs in Hong Kong. Clin Exp Pharmacol 2013; 3:124. doi. 10.4172/2161-1459.1000124.
30. López-Muñoz F, Castle DJ, Shen WW, Moreno R, Huelves L, Pérez-Nieto MA, *et al*. The Australian contribution to the literature on atypical antipsychotic drugs: A bibliometric study.

Australas Psychiatry 2013; 21:343-345.

31. López-Muñoz F, Sim K, Shen WW, Huelves L, Moreno R, Molina JD, *et al*. A bibliometric study of scientific research conducted on second-generation antipsychotic drugs in Singapore. Singapore Med J 2014; 55:24-33.
32. Price DJS. Little science, big science. New York: Columbia University Press; 1963.
33. Bradford SC. Documentation. London: Crosby Lockwood; 1948.
34. Garfield E. Citation indexing. Its theory and application in science, technology and humanities. New York: Wiley; 1979.
35. OECD Health Division. OECD Health Data 2013-Frequently Requested Data (November, 2013). Paris: OECD; 2013.
36. Pritchard A. Statistical bibliography or Bibliometrics. J Document 1969; 25:348-369.
37. Xiang YT, Kreyenbuhl J, Dickerson FB, Ungvari GS, Wang CY, Si TM, *et al*. Use of first- and second- generation antipsychotic medications in older patients with schizophrenia in Asia (2001-2009). Austral N Z J Psychiatry 2012; 46:1159-1164.
38. Grover S, Kumar V, Avasthi A, Kulhara P. First prescription of new elderly patients attending the psychiatry outpatient of a tertiary care institute in North India. Geriatr Gerontol Int 2012; 12:284-291.
39. Shen WW. Clinical Psychopharmacology for the 21 Century, the Third Edition (in Mandarin). Taipei: Ho-Chi Publishing Company; 2011.
40. Fountoulakis KN, Nimatoudis I, Iacovides A, Kaprinis G. Off-label indications for atypical antipsychotics: A systematic review. Ann Gen Hosp Psychiatry 2004; 3:4-14.
41. Mortimer AM, Shepherd CJ, Rymer M, Burrows A. Primary care use of antipsychotic drugs: an audit and intervention study. Ann Gen Psychiatry 2005; 4:18-26.
42. Gupta BM. Measurement of Indian Science and Technology using publications output during 1996-2010. Ind J Sci Technol 2012; 6:2899-2911.
43. Gupta BM, Bala A, Kshtig A. S&T publications output of India: A scientometric analysis of publications output, 1996-2011. Library Philosophy Practice (e-journal) 2013; Paper 921, http://digitalcommons.unl.edu/libphilprac/921.
44. Theander SS, Wetterberg L. Schizophrenia in Medline 1950-2006: A bibliometric investigation. Schizophr Res 2010; 118:279-284.
45. Mahadevan A. Indian pharmaceutical industry - Growth story to continue. Express Pharma 2012; 15 January.
46. Gupta BM, Bala A. A scientometric analysis of Indian research output in medicine during 1999-2008. J Nat Soc Biol Med 2011; 2:87-100.
47. Johnson MH, Cohen J, Grudzinskas G. The uses and abuses of bibliometrics. Rep BioMed Online 2012; 24:485-486.
48. Coleman R. Impact factors: use and abuse in biomedical research. Anat Rec 1999; 257:54-57.
49. Ha TC, Tan SB, Soo KC. The journal impact: too much of an impact. Ann Acad Med Singapore 2006; 35:911-916.
50. Warren CR, Serrato JJ, Maguire GA. Off-label uses of second-generation antipsychotics drugs: an overview. Taiwanese J Psychiatry 2012; 26:162-176.