

A Bibliometric Study of Scientific Research on Second-Generation Antipsychotic Drugs in Hong Kong

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Abstract

Background: We did a bibliometric study on the scientific publications on second-generation antipsychotic drugs (SGA) in Hong Kong.

Methods: With the EMBASE and MEDLINE databases, we chose those English articles from Hong Kong. We used bibliometric indicators of Price's law for the increase of scientific literature, and of Bradford's law for dispersion of papers. We also calculated the participation index of the different countries. Then, we correlated those bibliometric information with some social and health data (such as total per capita expenditure on health and gross domestic expenditure on research and development) of Hong Kong.

Results: Forty-four original papers were published between 1993 and 2011. Our results indicated non-fulfilment of Price's law (correlation coefficient $r=0.5597$ after exponential adjustment vs. $r=0.6725$ after linear adjustment). Those most widely studied SGA were clozapine (18 papers), risperidone (11 papers), and olanzapine (4 papers). Division into Bradford zones yielded a nucleus occupied by Journal of Clinical Psychopharmacology (4 articles) and Australian and New Zealand Journal of Psychiatry (4 articles). A total of 30 different journals were published.

Conclusion: The SGA publications in Hong Kong are still too few to confirm an exponential growth of scientific papers.

Keywords: Atypical antipsychotics; Bibliometry; Hong Kong; Schizophrenia; Second-generation antipsychotics

Introduction

Schizophrenia is a severe mental illness with prevalence ranging between 0.5% and 1.0% of the population [1]. The World Health Organisation (WHO) lists this illness among the top 10 disorders causing a significant disability particularly in the adult population [2].

After the introduction of chlorpromazine [3], the main therapeutic pillar for schizophrenia during the last 60 years is antipsychotic drugs. The first drugs, called first-generation (classical or typical) antipsychotic drugs, show a great efficacy in reducing positive symptoms of schizophrenia. But their main limitation is on their greater propensity to cause Extrapyramidal Side-Effects (EPS). The introduction of clozapine in 1960s in the United States dramatically changed the research expectations on antipsychotic drugs. Although clozapine had been previously withdrawn from the market due to its related agranulocytosis [4], its benefits on causing fewer EPS, having efficacy in both positive and negative symptoms from schizophrenia as well as its proven efficacy in patients who are refractory to other antipsychotic treatments [5], led to the later re-launch of clozapine back to the market. In the psychopharmacological aspect, clozapine has also opened up the door to the development of the so-called "atypical antipsychotics" [6] or Second-Generation Antipsychotic Drugs (SGAs) in the next following decades with the-introduction of risperidone in 1993.

The advances achieved in the development of antipsychotic drugs over the past 30 years have been revamped with the clinical use of various SGA (Table 1). SGA have notably improved the quality of life of psychiatric patients and have contributed decisively to weaken the stigmatization that has traditionally accompanied psychiatric

disorders [7]. After receiving their first licensed indication in treating schizophrenia-related disorders, and with their increasingly recognized efficacy in treating bipolar disorder, research on SGA have advanced considerably as translated into the considerable increase in SGA publications worldwide.

Hong Kong is a special administrative region of China, with her population reached around 7.07 millions in 2011 (Census and Statistics Department, HKSAR, 2012; <http://www.census2011.gov.hk/pdf/summary-results.pdf>). As one of the world's leading international financial centres, Hong Kong has a reputable capitalist economy. But the mental health policy in Hong Kong has been much less well organized. The total number of psychiatric beds in Hong Kong and the total number of in-patients treated in public hospitals had been reported to be 4,000 and 15,887, respectively in 2008-09. There were about 250 practising psychiatrists in Hong Kong as of March 2007, giving a psychiatrist-to-population ratio of 2/100,000 at that time [8], which was far lower than that of other developed countries like Australia (ratio of 14) and Japan (ratio of 9.4). Despite these pitfalls

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	Company	Launch	
		Year	Country
Clozapine	Wander Laboratories	1972 *	Switzerland
Zotepine	Fujisawa	1982 **	Japan
Amisulpride	Synthelabo	1986	Portugal
Risperidone	Johnson & Johnson	1993	UK / Canada
Sertindole	Abbott Laboratories	1996 ***	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

* Reintroduced in 1990 in USA and UK after being withdrawn from the market since 1975.

** Commercialized by Astellas in Germany in 1990.

*** 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 with extensive ECG monitoring requirement.

Table 1: Clinical development of second-generation antipsychotic drugs.

over the last decade, a gradual reform of the mental health services in Hong Kong has begun. A better training opportunity in psychiatry has driven the increase in the number of registered psychiatric specialists to 273 (Hong Kong Medical Council, 2012; <http://www.mchk.org.hk/doctor/Specialist/24.pdf>), giving the psychiatrist-to-population ratio of 3.9/100,000, a figure more comparable to other Asian developed countries like Taiwan (ratio of 4.1). Comprehensive patient care services, known as the Personalized Care Program, for patients with severe mental illness have also been launched territory-wide since 2012.

Bibliometric studies are useful tools for assessing the social and scientific relevance in a given discipline or field [9]. Our group has studied, with a bibliometric approach, the evolution of scientific literature in psychiatry by specific research groups, on different psychiatric disorders, on aspects related to the discipline, and on specific therapeutic tools in the field of psychopharmacology [10-16]. Here, we reported the results a bibliometric study on SGA publications in Hong Kong.

Methods

Data sources

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 databases participate in the EMBASE Biomedical Answer web (Elsevier B.V.).

With remote downloading techniques, we selected scientific articles published within 1993-2011 containing, in the Author Address (AD) section with the descriptor Hong Kong, and in the title (TI) section with the descriptors atypic* (atypical*), second-generation antipsychotic*, clozapine, risperidone, olanzapine, ziprasidone, quetiapine, sertindole, aripiprazole, paliperidone, amisulpride, zotepine, asenapine, iloperidone, lurasidone, perospirone and blonanserin. In this study, we looked up all the original articles, brief articles, reviews, editorials, letters to the editor, and other relevant communications published, with all duplicated publications being excluded.

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

Bibliometric indicators

The Price’s law [17] was applied as the bibliometric indicator of production in this study. This law reflects a fundamental aspect in scientific paper production, that is, whether its increase is of exponential growth. Linear adjustment—according to the equation $y=0.2982x - 0.6667$ ($r^2=0.4523$), and another adjustment to an exponential curve, according to the equation $y=0.0003e^{0.6308x}$ ($r^2=0.3133$) were used for the data obtained in order to assess if there was a growth of scientific publications on SGAs in Hong Kong and whether such growth followed the Price’s law.

Bradford’s law was also used to assess the dispersion of the scientific papers included in this study. 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 papers [18]. In other words, each Bradford zone would contain a similar number of articles, but the number of journals in which these articles were published would increase on passing from one zone to the next followed. This model permits identification of the journals most widely chosen for literature publication, or the journals with the greatest weight in a given field publishing scientific literature from Hong Kong.

The Impact Factor (IF) developed by the Institute for Scientific Information (Philadelphia, Pennsylvania, USA), which is published annually in the Journal Citation Reports (JCR) section of the Science Citation Index (SCI), was used as an indicator to reflect the identified SGA publication’s repercussion in the current study. IF is widely accepted as a quantitative tool for ranking, evaluating, categorizing, and comparing academic journals; and in turn, reflecting the quality of the submitted manuscripts and the studies reported. It is calculated based on a three-year period, and can be regarded as the average number of times published papers are cited up to two years after publication amongst journal titles sourced in the SCI database. The IF data of 2010 published in the JCR on 2011 was used in this study.

The index of collaboration between authors (signatures per document or authors per paper index) was also calculated. This index shows the quotient between the number of authors and the total number of scientific publications collected from the database.

Another indicator applied in this study was the national Participation Index (PI) of Hong Kong. PI on SGAs was the ratio between the number of articles published on SGAs by the Hong Kong researchers and the total number of scientific papers published. This PI was used to compare with the global PI in biomedical and health sciences, as well as the PI in Psychiatry and Neurology field. Moreover, the PI was used to correlate with the total per capita expenditure on health, and with the gross domestic expenditure on research and development (R&D) obtained from the Organisation for Economic and Co-operative Development (OECD) Health Division [19], and WHO Department of Health Statistics and Informatics [20]. The corresponding PIs from the world’s top 10 countries with the greatest scientific research publication outputs during the period of 1997-2011 were also shown for comparison.

Results

During the period of 1993-2011, 44 original papers dealing with

different aspects of SGAs in Hong Kong were retrieved. Of these, 18 papers were on clozapine, 11 on risperidone, 4 on olanzapine, 3 on quetiapine, 3 on paliperidone, 2 on ziprasidone, and 2 on amisulpride (some articles study various SGAs as a group and others not mention a specific SGA in the TI section). No article concerning aripiprazole, sertindole, asenapine, zotepine, iloperidone, lurasidone, perospirone, and blonanserin.

As shown in Figure 1, over the last 20 years there had been only a slight increase in the number of publications on SGAs in Hong Kong. The mathematical adjustments to the exponential and the linear curves confirmed that these data did not meet the postulates of Price's law. Figure 2 showed the growth of SGA papers during the last five-year period (2007-11) over the previous two five-year periods. The cumulative growth of SGAs publications in the previous two five-year periods was lower to the total growth of publications in biomedicine and health sciences, and in Psychiatry and Neurology. However, there noted a higher cumulative increase in publications on SGAs in the latest five-year period than the other two fields.

Analysis using the Bradford's model for journals in which the SGA papers were published (Table 2) demonstrated that after discarding the last zone, with the expected frequency of 10 articles per Bradford zone, the mean number of articles identified was obviously lower. The nucleus of the first zone was with articles published in the Journal of Clinical Psychopharmacology (n=4 articles) and in the Australian and New Zealand Journal of Psychiatry (n=4). The rest of the journals analysed was located in zones 2 to 6. Of these 30 different journals, four journals, which all had IF greater than 2, had published 31.82% of all the identified papers in the current study (Table 3).

Using manual categorisation, 40.9% of the retrieved publications belonged to the "tolerance and safety" group, 34.1% to the "clinical efficacy" group, 9.1% to the "experimental pharmacology" group, and 15.9% to the "not specified" group, concerning pharmaco-economic analysis and prescription patterns. Articles on clinical studies were mainly devoted to the diagnosis of schizophrenia (n=9).

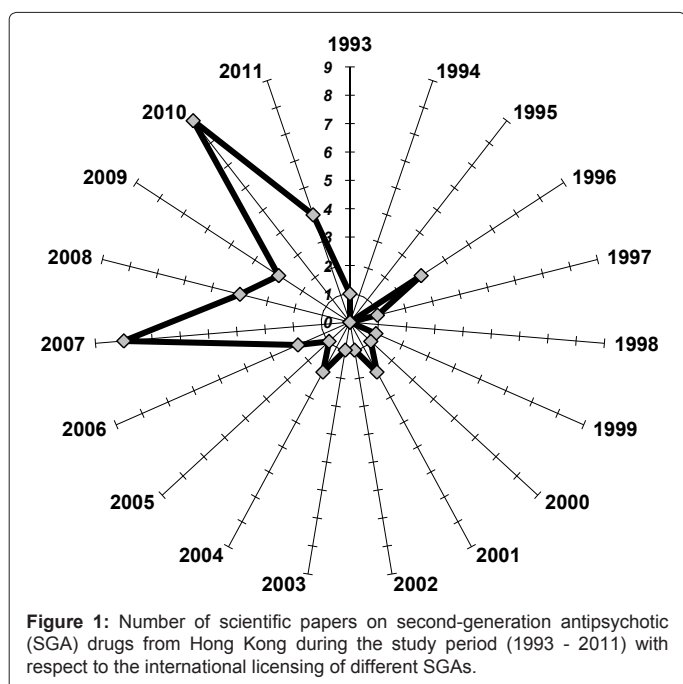


Figure 1: Number of scientific papers on second-generation antipsychotic (SGA) drugs from Hong Kong during the study period (1993 - 2011) with respect to the international licensing of different SGAs.

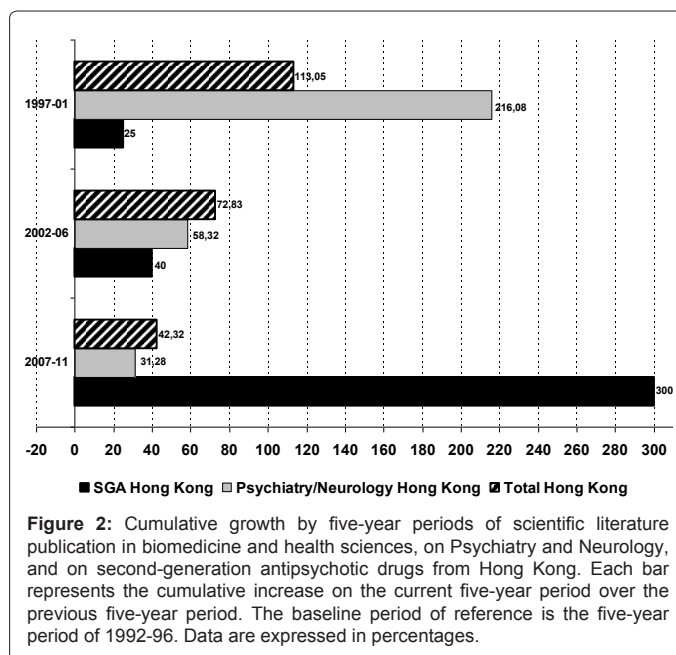


Figure 2: Cumulative growth by five-year periods of scientific literature publication in biomedicine and health sciences, on Psychiatry and Neurology, and on second-generation antipsychotic drugs from Hong Kong. Each bar represents the cumulative increase on the current five-year period over the previous five-year period. The baseline period of reference is the five-year period of 1992-96. Data are expressed in percentages.

Zones	Number of journals	Number of articles	Bradford's constants
1	2	8	
2	3	8	1.5
3	5	8	1.67
4	8	8	1.6
5	8	8	1
6	4	4	

Total number of journals = 30
 Average number of articles = 7.33
 Average number of articles, excluding the last Bradford zone = 8

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

Journal	N° Documents	PI	IF*
Journal of Clinical Psychopharmacology	4	9.09	4.857
Australian and New Zealand Journal of Psychiatry	4	9.09	2.418
International Journal of Neuropsychopharmacology	3	6.82	4.699
Journal of Psychopharmacology	3	6.82	3.801

PI, participation index; IF, impact factor 2010
 *Journal Citation Report, 2010 (JCR, 2011).

Table 3: The four journals with the greatest number of publications on second-generation antipsychotic drugs from Hong Kong.

The collaboration index (quotient of studies with n co-authors), indicative of the collaboration of authors in the preparation of the manuscript, was 6.21 authors per paper in the 2007-11 five-year period. The collaboration indices were 2.75 in the 1992-96 five-year period, 4 in the 1997-2001 five-year period, and 6.86 in the 2002-06 five-year period. This signified an increase of 125.8% of authors' collaboration when SGA articles were prepared over this 20-year study period.

The contribution of publications on SGAs to biomedicine and health sciences in Hong Kong represented a global PI of 0.23 during the study period. Table 4 and Figure 3 show the comparisons on the proportions of scientific paper publications on SGAs to the proportions of publications in biomedicine and health sciences, and in the field of Psychiatry and Neurology, between the world's top 10 most "productive" countries and Hong Kong. Similar to Japan, another well-developed capitalist economy in the Asia Pacific region, Hong

	Country *	% *	Psy-Neurol ** (%)	SGAs (%)	SGAs/Psy-Neurol
1	USA	25.78	35.61	31.84	1.14
2	UK	7.36	9.92	7.97	1.01
3	Japan	6.62	6.82	3.27	0.61
4	Germany	6.30	7.93	6.33	1.02
5	France	4.55	4.93	3.46	0.89
6	China	3.95	2.90	2.00	0.88
7	Italy	3.87	4.76	4.59	1.23
8	Canada	3.67	5.03	5.68	1.44
9	Spain	2.69	2.90	3.93	1.73
10	Australia	2.47	3.07	2.69	1.12
	Hong Kong	0.47	0.46	0.23	0.65

Psy-Neurol, area of focus in Neurology and Psychiatry; SGAs, second-generation antipsychotic drugs.

* The world's top 10 most productive countries in biomedicine and health sciences for the period 1993-2011.

** The "productivity" in the discipline of Psychiatry and Neurology.

Total documents 1993-2011: 13,746,667

Total documents in Neurology & Psychiatry Area 1993-2011: 1,471,156

Table 4: Distribution of literature on second-generation antipsychotic drugs from the world's top 10 most productive countries in biomedicine and health sciences compared to Hong Kong for the study period (1993-2011).

Kong appeared occupying only at the bottom rank with respect to SGA publications.

Figure 4 demonstrates the relationship between publication of SGA scientific papers and per capita health expenditure, and gross domestic expenditure on R&D in Hong Kong, as well as compared to those among the world's 10 most "productive" countries in biomedicine and health sciences publications. Despite having moderate per capita health expenditure, the relative contribution from Hong Kong on SGA studies was small and was well behind the other 10 countries.

Further analyses revealed that the Chinese University of Hong Kong had contributed the greatest number of SGAs publications (n=6) during the study period, followed by the Queen Mary Hospital (n=5), the Castle Peak Hospital (n=4), and the Shatin Hospital (n=4). These four centres accounted for 43.18% of the total SGA articles published from Hong Kong.

Discussion

Previous bibliometric studies had drawn attention to a series of limitations specific to this sociometric approach [21]. Grey literature is one of the common criticisms. Nevertheless, with the extensiveness of the two search databases attained, and the diversities in categories of the SGA articles generated in our study, the coverage of the publications identified should have constituted a more than the representative sample of the international research on SGAs from Hong Kong.

The design of the present analysis permitted a global assessment on the growth of SGA scientific publications in Hong Kong. Although the number of scientific papers had increased substantially in recent years, the growth was not exponential, with the correlation coefficient $r=0.5597$ after exponential adjustment vs. $r=0.6725$ after linear adjustment. Such finding was different from the results of our earlier studies from Taiwan [14], South Korea [15] and Japan [16], where both showed exponential growths in SGA research publications. Since the variety of SGA prescriptions has been demonstrated with a significant increase over the years in the Research on Asian Psychotropic Prescription (REAP) Project (45.5% in 2001, 64.7% in 2004, and 76.6% in 2008) [22], it might be meaningful to understand why Hong Kong did not show a similar exponential growth as Taiwan and Japan did.

We speculated that despite 15 SGAs were included in the current literature search, only nine of them, namely, amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, sertindole and ziprasidone have been licensed and available in Hong Kong during the study period. This might bound the numbers and variety of SGA research carried out in Hong Kong, leading to a small sample size in terms of publications identified, and thus limiting the application of the Price's law in this study.

The surge in scientific research and publications on SGAs appeared to coincide with their approved indications for various psychiatric disorders from the medicine regulatory agencies, such as the US Food and Drug Administration and the European Medicines Agency. Previously, Clement et al. [23] had reported that schizophrenia is superior to other diagnoses in research activities using the bibliometric analysis. Theander and Wetterberg [24] had subsequently reported that the number of references on schizophrenia in MEDLINE had followed the general increase in medical publications, accounting for 0.42% of all medical literature published from 1950 to 2006. Thus, it would not be surprising if research in the past on SGAs had been more localized on schizophrenia since antipsychotics have always been its mainstay of treatment. Nevertheless, except amisulpride, clozapine, paliperidone and sertindole, all the other five SGAs (aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone) currently available in Hong Kong have been licensed in treating bipolar disorder as well [25], with quetiapine also acquired its recent approvals as monotherapy agent for treating major depressive disorder and generalized anxiety disorder. As noted by our earlier studies [14-16], scientific research on SGAs has been one of the fastest growing fields in psychiatry. And with a growing number in overseas research studies and publications on "off-labelled" use of SGAs, including toxic psychosis, agitation symptoms, tics disorders, and substance abuse disorders [26,27], it could therefore be expected that future bibliometric analysis for SGAs-related publications from Hong Kong might show a catch-up growth following the Price's law.

Another aspect of interest for the current study in relation to the scientific publication on SGAs from Hong Kong was to investigate on its research paper quality. In recent years, journals such as the *Journal of Clinical Psychopharmacology* (IF=4.857), the *International Journal of Neuropsychopharmacology* (IF=4.699), and the *Journal of Psychopharmacology* (IF=3.801) had published SGA-related articles from Hong Kong. To note, the top four journals which published more than one third of all the identified articles carried the IFs being greater than 2.00 having their significant impacts in the field of psychiatry, SGA research and their related publications from Hong Kong could be regarded as increasingly better in quality and more important internationally.

Both English-speaking countries (the US and the United Kingdom) had contributed 39.81% of all the scientific papers in Psychiatry & Neurology (Table 4). Housing the headquarters of those pharmaceutical companies that are responsible for the development of several commonly used SGAs (olanzapine, Eli Lilly; risperidone and paliperidone, Janssen Pharmaceutica; quetiapine, AstraZeneca; ziprasidone, Pfizer; aripiprazole, Bristol-Myers Squibb/Otsuka Pharmaceutical), it might help explain their high PIs. But as illustrated in Figure 3, countries such as Canada and Spain had showed a positive growth on SGA publications with respect to those in the Psychiatry & Neurology field. This might reflect their special interests in research on SGAs irrespective to their sites of development. Thus, it would be interesting to explore the reason for Hong Kong's bottom-ranking on her PI despite her Excellency in research on early psychosis [8].

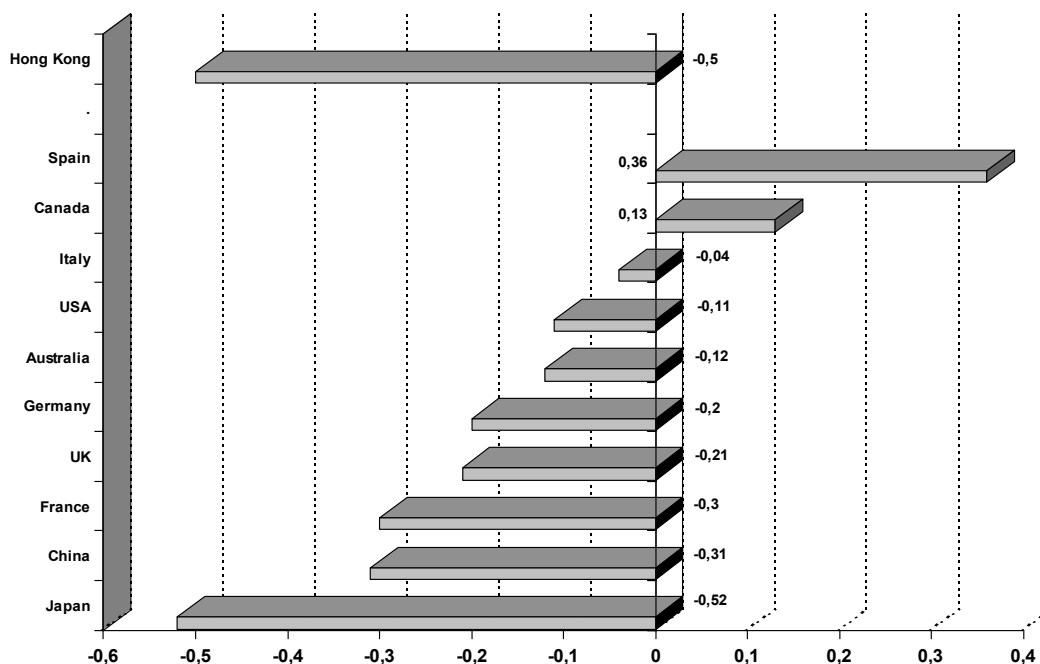


Figure 3: Graphical representation on the comparisons on publications on second-generation antipsychotic drugs to those in the field of Psychiatry and Neurology between the world's top 10 most productive countries in biomedicine and health sciences and Hong Kong. PI, participation index; SGAs, second-generation antipsychotic drugs.

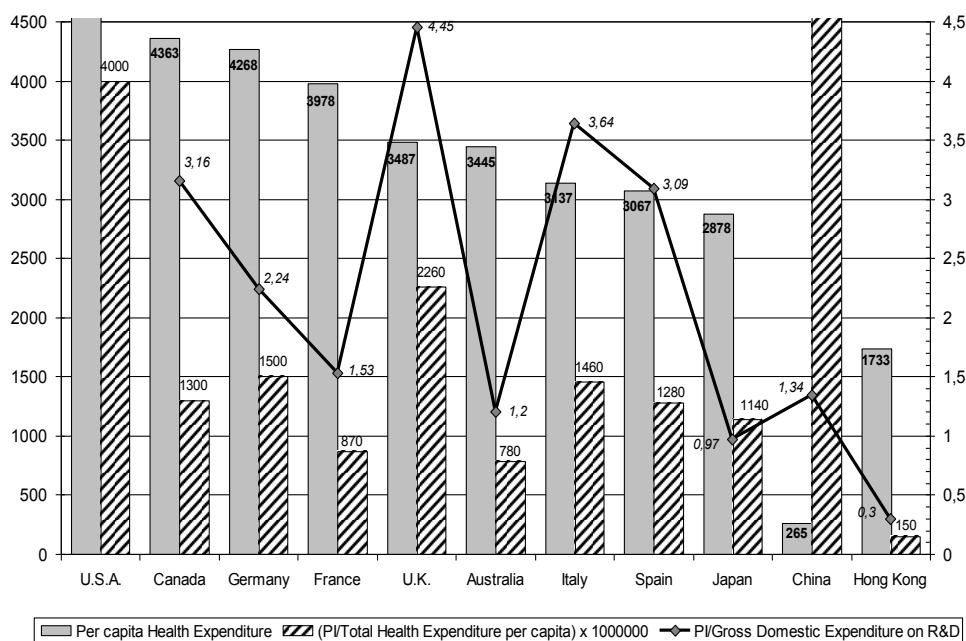


Figure 4: Per capita health expenditure and its relationship between publications of scientific literature on second generation antipsychotic drugs and per capita health expenditure and gross domestic expenditure in relations to research and development among the world's top 10 most productive countries in biomedicine and health sciences compared to those from Hong Kong. PI, participation index.

Total Health Expenditure per capita PPP US \$, data from Organisation for Economic and Cooperative Development 2009 [19].

Japan and Australia; Data 2008

China: Total Health Expenditure per capita PPP Int \$ (data 2008) [20].

Hong Kong: Total Health Expenditure per capita US \$ (data Department of Health: http://www.dh.gov.hk/english/statistics/statistics_hs/files/Health_Statistics_pamphlet_E.pdf).

Gross Domestic Expenditure on R & D (%). Data OECD 2010, except USA and Japan (data 2009) and China (data 2007).

Hong Kong: Data of Census and Statistical Department (http://www.censtatd.gov.hk/hong_kong_statistics/statistics_by_subject/index.jsp?subjectID=7&charsetID=1&displayMode=T).

The correlation of scientific papers on SGAs with the per capita health expenditure for each country (Figure 4) might offer another explanation of the phenomenon on why Hong Kong had a low PI on SGA research. In general, one would expect that the higher the expenditure on health, the greater would be the health research-related activities. It was therefore striking to observe such low ratios for countries such as Australia, France, and especially for Hong Kong. Being one of the world's highest gross domestic product per capita city (PPP US\$ 49,137), Hong Kong has been reported only having 5.5% of her gross domestic product spent on healthcare, out of which only about 0.24% distributed to mental health [8]. The correlation analysis between the scientific SGA research publications and the gross domestic expenditure on SGA research and development in our current study also demonstrated such an exceptionally low ratio for Hong Kong. The lack of public research funding in Hong Kong reported by Cheung et al. [8] might have pinpointed the core of this situation.

Limitations and strengths of the study

Readers might have to be cautioned against generalizing the current study findings because this study has three major limitations in common to other bibliometric studies [20]. First, not all SGA papers from Hong Kong were included in this study. This bibliometric study included papers retrieved only from the EMBASE Biomedical Answer web. The search fields constrained by the databases themselves have restrained the subsequent development of the studied materials [28,29]. We might then have excluded those papers on SGAs if the authors have 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 Hong Kong's investigators at scientific conferences and meetings were also not included in our current study [29]. In fact, the *East Asian Archives of Psychiatry* (previously titled as the *Hong Kong Journal of Psychiatry* before March 2010), which is the official peer-reviewed publication of the Hong Kong College of Psychiatrists since 1991, has only been indexed in MEDLINE since 2011. Second, in the AD section using the descriptor "Hong Kong", we included those papers with authors specifying "Hong Kong" in their addresses only. We did not count those papers as Hong Kong papers if the contributor authors from Hong Kong had not put their Hong Kong addresses. Finally, the use of the SCI impact factor to determine the merit or quality of scientific contributions is still 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". This might explain why most universities of the United States, unlike those in Europe and in Asia, do not usually use impact factor to evaluate the academic outputs of their faculty members.

Nevertheless, in spite of the above-listed major limitations swirling around bibliometric studies, they are still considered useful in assessing the social and scientific relevance of a given discipline or field [9]. Bibliometric studies remain to be important in constituting an effective complement for the opinions and judgments of experts in each field, in providing a useful and objective measure to evaluate the results of the scientific activity, in offering a more realistic view of the global picture and as an indication of the trends of research in one specific discipline, as well as in predicting how the research activity might evolve for a given scientific speciality [30].

In conclusion, our current study offered an opportunity to unveil the recent changes of the representativeness and growth of

publications concerning the research on SGAs in Hong Kong. Having demonstrated the better quality and wider dissemination of scientific research literature on SGAs from Hong Kong, it could be expected that research in this field would possibly continue to grow in the future since the "ideal" antipsychotic drug has not yet been found [7], that etiopathogeny of schizophrenia remains unclear, and there have been broader licensed indications for SGAs used in treating psychiatric disorders in Hong Kong.

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