Int. J. Pharm. Investigation, 2023; 13(1):14-21.
www.jpionline.org

Review Article

Clozapine: A Scientific Analysis of Global Publications during 1970-2021

Sandeep Grover[1,*], B.M. Gupta[2], K.K. Mueen Ahmed[3], Yogindra Singh[4]

[1]Department of Psychiatry, Post Graduate Institute of Medical Education and Research, Chandigarh, INDIA.
[2]Formerly with CSIR-NISTADS, New Delhi, INDIA
[3]Phcog.Net, Cox Town, Bengaluru, Karnataka, INDIA.
[4]Swami Rama Himalayan University, Dehradun, Uttarakhand, INDIA.

ABSTRACT

Aim: This study evaluates the research output on Clozapine included in Scopus database during 1970-2021. **Materials and Methods:** The quantitative and qualitative analysis of publications on "Clozapine" covered in Scopus database during 1970-2021 was undertaken. The results obtained were further analysed using additional features in Scopus database. **Results:** 7399 publications on "Clozapine" were obtained from Scopus international database and these publications received 189068 citations, averaging 25.55 citations per paper (CPP). There was initial rise in the number of publications per year from 1988 to 1995, after that the number of publications has remained relatively stable. Authors from USA, U.K. and Germany contributed to the largest number of publications (2136, 709 and 457 publications respectively), and publications with authors from USA, Canada and Germany registered the highest CPP and relative citation index (RCI). The authors from King's College London, U.K, The Zucker Hillside Hospital, USA and University of Toronto, Canada published the highest number of publications. The organization that registered the highest CPP and RCI was Sandoz International GmbH, Switzerland, Long Island Jewish Medical Centre, USA and Vanderbilt University, School of Medicine, USA. The authors who published the highest number of publications were H.Y. Meltzer (USA), J.A. Lieberman (USA) and A. Weizman (Israel). The authors who registered the highest CPP and RCI were R.W. Kerwin (U.K.) and J.P. Lindermayer. The journals that published the highest number of publications were *Journal of Clinical Psychopharmacology (351 papers), Journal of Clinical Psychiatry (282 papers),* and *American Journal of Psychiatry (255 papers). The* most impactful publications were published in *Archives of General Psychiatry*, *Schizophrenia Bulletin*, *Journal of Pharmacology* and *Experimental Therapeutics*, and *American Journal of Psychiatry.* **Conclusion:** This study suggests that the numbers of publications on clozapine have remained stable over the years and maximum research has emerged from the developed countries.

Keywords: Clozapine, Atypical antipsychotics, Bibliometrics, Scientometrics.

Correspondence
Prof. Sandeep Grover
Department of Psychiatry, Post Graduate Institute of Medical Education and Research, Chandigarh, INDIA.
Email id: drsandeepg2002@yahoo.com
ORCID ID 0000-0002-2714-2055

Received: 25-08-2022;
Revised: 16-10-2022;
Accepted: 02-11-2022.

INTRODUCTION

Clozapine was synthesized in 1958, and was described as tricyclic antidepressants with neuroleptic properties. In the initial evaluation as an antipsychotic, it was seen with scepticism, because of lack of extrapyramidal side effects.[1] However, within four months of introduction in Finland, there emerged a report that brought into light 18 patients who developed one or more severe blood disorders, 9 of whom died. Sixteen of these patients developed agranulocytosis.[2] This led to withdrawal of clozapine from many European countries and its use decreased significantly worldwide.[1] The resurgence in the use of clozapine started with its use in patients with treatment resistant schizophrenia (TRS) in 1989, after it was approved by the United States Food and Drug Administration. In this initial trial Kane *et al.*,[3] showed that clozapine was significantly more effective than chlorpromazine in patients who failed to respond to multiple adequate trials of different antipsychotics.[3] After this trial, use of Clozapine increased and its use was limited to patients with TRS. Over the years, the definition of TRS has been revised by different researchers, authors and organization.[4] Although these attempts have been towards increasing clozapine use in clinical practice, it is still considered to be underutilized. Available data suggests that starting of clozapine is often delayed by 1.5 to 2 years.[5]

Over the years many reviews and meta-analysis have evaluated the effectiveness and side effect data for clozapine.[6-12] However, these publications do not provide information about the publication trends on clozapine. Bibliometrics can provide important information about the publication trends, authors involved in the research, country of origin of the authors

DOI: 10.5530/223097130001

and the publications and citation for the publications. In contrast to multiple systematic reviews and meta-analysis on various aspects of clozapine, there is only one bibliometric study that has exclusively focused on clozapine. In this study authors examined global publications (5607 records) on clozapine published during the period of 1970-2013, indexed in Embase and Medline databases.[13] The authors focused and highlighted the contribution of authors from different countries, organizations, and journals. It was evident from the analysis, that maximum number of publications on clozapine emerged from USA, followed by UK and Germany.[13] This bibliometric analysis showed that the difference in clozapine research across different countries was significantly related to economic variables linked to research.[13] Considering the fact that this bibliometric study evaluated data up to 2013, there is a need to carry out an updated bibliometric study on clozapine. Accordingly, this bibliometric study aimed to evaluate the research output on clozapine published during the period of 1970-2021 in terms of number of publications, citation impact, and contribution by different authors, most productive and cited organizations and authors, important journals contributing on this topic and characteristics of high-cited papers.

MATERIALS AND METHODS

Publications listed in the Scopus database (https://www.scopus.com) were searched by using 'clozapine" as the keyword in the 'keyword' and the 'title tag'. The articles were identified, retrieved and downloaded. The search was limited to publication years 1970-2021, but was not limited to English language only. The analytical provisions as provided in the Scopus database were utilized to ascertain the distribution of publications by broad subject areas, collaborating countries, contributing authors, affiliating organizations and the journals in which the articles were published. The citations to publications were counted from date of their publication till 14.2.2022. The study used different metrics and indicators to quantify and evaluate the performance of the most productive organizations, authors and journals.

Table 1: Total Annual Publications on "Clozapine" during 1970-2021.

Year	TP	Year	TP	Year	TP	Year	TP
1970	1	1984	19	1998	267	2012	198
1971	3	1985	16	1999	263	2013	199
1972	2	1986	18	2000	226	2014	220
1973	12	1987	21	2001	226	2015	234
1974	40	1988	32	2002	168	2016	245
1975	37	1989	69	2003	188	2017	228
1976	31	1990	94	2004	208	2018	212
1977	36	1991	113	2005	199	2019	251
1978	30	1992	176	2006	194	2020	276
1979	20	1993	189	2007	228	2021	325
1980	19	1994	284	2008	174	1970-2021	
1981	8	1995	258	2009	194		
1982	10	1996	277	2010	196		
1983	12	1997	250	2011	203		

*TP= Total publications.

ANALYSES AND RESULTS

The search yielded 7399 records on "Clozopine" published during the last 52 years (1970-2021) as indexed in Scopus database. In the year 1970 only 1 paper was published on clozapine, which increased to 325 publications in 2021, registering an annual average growth rate of 24.81%. There was gradual increase in number of publications from 1970 to 1988 with some fluctuations in total number of publications. However, from 1989 onwards, the number of publications was more than 100 in a given year (Table 1). These 7399 publications received 1, 89, 068 citations averaging citations per paper (CPP) of 25.55 (Table 2).

When the number of publications were analysed in terms of various blocks of years, there were only 58 publications from 1970-1974, which increased over the next 12 years to only 277. However, over the next 12 years, the total number of publications increased by 9 times to 2498; after this for subsequent block of 12 years the number of publications remained relatively stable to 2376; and in the final 10 years the number of publications was 2190. Maximum numbers of high-cited papers (cited at least 100 times) were published during the period of 1988 to 2000 (Table 2).

About one-sixth (16.07%) of the publications were based on funded research. These 1189 funded publications received 55,167 citations, averaging CPP of 46.4. The largest number of funded papers were supported by National Institute of Mental Health, USA (441 papers), and National Institute of Health, USA (399 papers) (Table 3).

Of the 7399 global publications, 68.33% (n=5056) appeared as articles, and these were followed by letters (18%; n=1329), reviews (6.47%; n= 471), short surveys (2.6%; n= 190), conference papers (2.1%, n=154), notes (2%, n=150), and the other publications (erratum, editorial and book chapters) accounting for 1% of

Table 2: Publications and Citations of "Clozapine" Publications published during 1970-2021.

Publication Years	TP	TC	CPP	FP	FP	HCP	Growth rate
1970-1974	58	1363	23.5	0		3	225
1975-1987	277	8271	29.9	30	2.52	22	0.3
1988-2000	2498	105623	42.3	326	27.42	242	22.1
2001-2011	2376	65362	27.5	354	29.77	114	-0.23
2012-2021	2190	20127	9.2	479	40.29	13	6.72
1970-2021	7399	189068	25.5	1189		394	24.8

TP= Total publications; TC= Total citations; CPP= Citations per paper; FP= funded papers; HCP -High cited papers.

Table 3: List of Funding Agencies Supporting Research in "Clozapine".

Sl. No	Name of the Funding Agency	TP	TC	CPP
1	National Institute of Mental Health, USA	441	35057	79.5
2	National Institute of Health, USA	399	29715	74.5
3	U.S. Department of Health and Human Service,	314	27431	87.4
4	National Institute of Drug Abuse, USA	71	3835	54
5	National Alliance for Research on Schizophrenia and Depression	54	2366	43.8
6	Canadian Institute of Health Research	47	972	20.7
7	Medical Research Council	47	1946	41.4
8	U. S. Public Health Service	46	2428	52.8
9	Eli Lilly and Company	42	1304	31.1
10	National Health and Medical Research Council	41	1192	29.1

TP= Total publications; TC= Total citations; CPP= Citations per paper.

total publications. Majority of the publications (*n*=6726) were published in English, followed by those published in German (*n*=136; 1.8%), French (*n*=126; 1.7%), Spanish (*n*=85;1.1%), Dutch (*n*=82;1.1%), Chinese (*n*=72; 1%), Indian languages (*n*=31;.4%), Portuguese and Turkish (*n*=24 each;0.3%), and Polish (*n*=23;0.3%), etc.

On further analysis, it was evident that out of the 7399 global publications, 2080 publications were controlled studies, and this was followed by case reports (*n*=1900), clinical trials (*n*=742), retrospective studies (*n*=370), comparative studies (*n*=334), controlled clinical trials (*n*=317), randomized controlled trials (*n*=254) and systematic reviews (*n*=90).

In terms of subject of research, 2581 publications were clinical studies, 1065 publications focused on treatment outcome, 632 focused on side effects, 253 on risk factors, 250 focused on pathophysiology and 159 focused on genetics.

Contribution from Top 10 Countries

Analysis of country-wise data revealed that publications on clozapine have emerged from 104 countries across the world. Maximum number of publications emerged from USA, followed by UK, Germany, Canada, Australia and Italy. Authors from top 10 countries in terms of number of publications contributed to 231 to 2,136 papers. Together, authors from top 10 countries contributed 5,387 publications and these papers were cited 17, 15, 06 times, constituting to 72.81% and 90.71% share of the total publications and citations related to clozapine. On further analysis, it was evident that authors from only two countries (USA and UK) had more than the average productivity (538.7) of the top 10 countries (Table 4).

Diagnostic Groups and clozapine

When the publications on clozapine were analysed in terms of diagnostic groups, it was seen that about two-third of the publications focused on schizophrenia. However, in about one-third of the publications, the other diagnostic groups were considered and these included schizoaffective disorders, Parkinson's disease, Bipolar Disorder, Suicidal Behaviour, Obsessive Compulsive Disorder and Personality disorders (Table 5). If the articles focused on more than one diagnostic group and had a schizophrenia group, the articles were included in the schizophrenia group. However, if the articles focused on specific issues like suicidal behaviour or obsessive compulsive features, these were categorised separately.

Table 4: Profile of Top 10 Most Productive Countries in "Clozapine" Research.

Sl. No	Country name	TP	TC	CPP	HI	ICP	%ICP	RCI
1	USA	2136	94553	44.27	140	373	17.46	1.7
2	U.K.	709	17476	24.65	67	216	30.47	1
3	Germany	457	12874	28.17	62	109	23.85	1.1
4	Canada	409	14794	36.17	57	149	36.43	1.4
5	Australia	398	7570	19.02	44	106	26.63	0.7
6	Italy	308	7647	24.83	49	58	18.83	1
7	France	257	5272	20.51	28	33	12.84	0.8
8	India	244	2971	12.18	22	39	15.98	0.58
9	China	238	3721	15.63	29	87	36.55	0.6
10	Netherlands	231	4628	20.03	38	66	28.57	0.8
	Total of 10 top countries	5387	171506	31.84	536	1236	22.94	1.2
	Global total	7399	189068	25.55				
	Share of top 10 countries in global total	72.81	90.71					

TP= Total publications; TC= Total citations; CPP= Citations per paper; ICP: International Collaboration papers; RCI: Relative Citation Index (based on weighting the number of citations a paper receives to a comparison group within the same field).

Table 5: Diagnostic Groups and "Clozapine" Publications.

Sl. No	Name of the disease	TP	%TP
1	Schizophrenia	4657	62.9
2	Schizoaffective Disorders	341	4.6
3	Parkinson's Disease	260	3.5
4	Bipolar Disorder	255	3.5
5	Suicidal Behaviour	136	1.8
6	Obsessive Compulsive Disorders	101	1.4
7	Personality Disorders	53	0.7
8	Other conditions	262	3.5
9	Global total	7399	

TP=Total publications.

Contribution by Top 50 Organizations

Overall, publications on clozapine emerged from 2082 organizations. The top 50 most productive organizations contributed 32 to 203 publications, and together contributed 2819 publications and 1,18,939 citations, accounting for 38.1% and 62.9% share of global publications and citations, respectively. Of the top 50 organizations, 20 were from USA, 4 each from Australia and Germany, 2 each from Canada, China, India, Israel, Netherlands, Spain and U.K. and 1 each from Brazil, Denmark, Finland, Italy, Singapore, Sweden, Switzerland and Turkey. The King's College London, U.K. was the most productive organization. In terms of most impactful organization, Sandoz International GmbH, Switzerland topped the list. Table 6 presents the list of top 10 most productive and 10 most impactful organizations.

Contribution by Top 50 Authors

Overall, 3851 authors participated in "clozapine" research, of which 2789 authors published 1-5 papers each, 867 authors published 6-10 papers, 145 authors published 11-20 papers, 31 authors published 21-30 papers, 11 authors published 31-40 papers, 4 authors published 41-50 papers and 4 authors 51-140 papers each. The top 50 most productive authors individually contributed 21 to 140 papers and together contributed 1,669 publications and 86,783 citations, accounting for 22.83% and 45.9% share of total publications and citations, respectively. Of the top 50 authors, 22 were from USA, followed by 5 each from Canada and U.K., 3 each from Australia and Netherlands, 2 each from India and Taiwan and 1 each from Austria, Germany, Israel, Italy, Denmark, Spain and South Korea. The most productive authors is H.Y. Meltzer, followed by J. A. Lieberman, A. Weizman, G. Ramington and D. Siskind. In terms of most impactful authors, R.W. Kerwin topped the list, and he was followed by J.P. Lindermayer, A. Breier and J.A. Lieberman. Table 7 presents the list of top 10 most productive and 10 most impactful authors.

Contribution by Top 50 Journals

Out of the all publications on clozapine, 7346 publications were published in 802 journals, 15 in books, 11 in book series, 6 in conference proceedings, 5 in trade journals and 6 as undefined. Among the 802 journals, 537 journals published 1-5 papers each, 135 journals published 6-10 papers, 64 journals published 11-20 papers, 21 journals published 21-30 papers, 12 journals published 31-40 papers, 10 journals published 41-50 papers, 16 journals published 51-100 papers and 7 journals published 101-351 papers. The top 50 most productive journals individually published 27 to 351 papers and together published 3696 papers

Table 6: Profile of Top 10 Most Productive and Most Impactful Organizations in "Clozapine" Research during 1970-2021.

Sl. No	Name of the organization	TP	TC	CPP	HI	ICP	%ICP	RCI
Top 10 Most Productive Organizations								
1	King's College, London, U.K.	203	6857	33.78	47	88	43.35	1.3
2	The Zucker Hillside Hospital, USA	137	7592	55.42	46	60	43.80	2.2
3	University of Toronto, Canada	133	6597	49.60	41	67	50.38	1.9
4	South London Maudsley NHS Foundation, U.K.	123	3184	25.89	27	42	34.15	1
5	Harvard Medical School, USA	114	6320	55.44	38	21	18.42	2.2
6	V A Medical Center, USA	91	3796	41.71	31	8	8.79	1.6
7	Tel Aviv University, Israel	83	2910	35.06	32	21	25.30	1.4
8	The University of British Columbia, Canada	73	2044	28.00	22	14	19.18	1.1
9	Maryland Psychiatric Research Center, USA	68	3186	46.85	30	14	20.59	1.8
10	Massachusetts General Hospital, USA	68	3896	57.29	31	14	20.59	2.2
Top10 Most Impactful Organizations								
1	Sandoz International GmbH, Switzerland	39	7278	186.62	27	23	58.97	7.3
2	Long Island Jewish Medical Center, USA	40	3827	95.68	28	2	5	3.7
3	Vanderbilt University, School of Medicine, USA	32	2490	77.81	21	6	18.75	3
4	National Institute of Mental Health, USA	63	4840	76.83	40	3	4.76	3
5	Nathan Skline Institute of Psychiatric Research, USA	45	3069	68.2	30	12	26.67	2.7
6	Karolinska Institute, Sweden	64	4269	66.7	29	27	42.19	2.6
7	Albert Einstein College of Medicine at Yeshiva University, USA	54	3329	61.65	28	9	16.67	2.4
8	The Case Western Reserve University, USA	56	3307	59.05	29	4	7.14	2.3
9	Massachusetts General Hospital, USA	68	3896	57.29	31	14	20.59	2.2
10	National Institute of Health, USA	34	1935	56.91	23	7	20.59	2.2

TP= Total publications; TC= Total citations; CPP= Citations per paper; HI= H-Index; ICP: International Collaboration papers; RCI: Relative Citation Index.

Table 7: Profile of Top 10 Most Productive and Most Impactful Authors in "Clozapine" Research during 1970-2021.

Sl. No	Name of the author	Affiliation of the author	TP	TC	CPP	HI	ICP	%ICP	RCI
Top 10 Most Productive Authors									
1	H.Y.Meltzer	Northwestern University Feinberg, School of Medicine, Chicago	140	13038	93.13	54	35	25.00	3.6
2	J.A. Lieberman	The Zucker Hillside Hospital, USA	83	8315	100.18	46	26	31.33	3.9
3	A. Weizman	Tel Aviv University, Israel	56	1764	31.50	24	8	14.29	1.2
4	G.Remington	University of Toronto, Canada	53	1973	37.23	20	25	47.17	1.5
5	D.Siskind	University of Queensland, Australia	49	1063	21.69	14	29	59.18	0.8
6	J.M.Kane	The Zucker Hillside Hospital, USA	47	3646	77.57	31	9	19.15	3
7	D.L.Kelly	Maryland Psychiatric Research Center, USA	46	1107	24.07	18	9	19.57	1
8	D.Taylor	South London Moudsley NHS Foundation Trust, U.K.	41	1621	39.54	19	11	26.83	1.5
9	J.H.MacCabe	King's College London, U.K.	40	570	14.25	14	21	52.50	0.6
10	J.Nielsen	Aalborg Universites hospital, Denmark	39	1413	36.23	19	28	71.79	1.4
Top 10 Most Impactful Authors									
1	R.W.Kerwin	King's College London, U.K.	30	4097	136.57	28	13	43.33	5.3
2	J.P.Lindermayer	Manhatten Psychiatric Center, USA	22	2738	124.45	14	1	4.55	4.9
3	A.Breier	National Institute of Mental Health, USA	24	2481	103.38	21	1	4.17	4
4	J.A. Lieberman	The Zucker Hillside Hospital, USA	83	8315	100.18	46	26	31.33	3.9
5	A.Z.Safferman	The Zucker Hillside Hospital, USA	22	2164	98.36	15	1	4.55	3.8
6	D.C.Goff	Massachusetts General Hospital, USA	29	2749	94.79	23	2	6.9	3.7
7	H.Y.Meltzer	Northwestern University Feinberg, School of Medicine, Chicago, USA	140	13038	93.13	54	35	25	3.6
8	R.W.Buchanan	Maryland Psychiatric Center, USA	26	2281	87.73	20	1	3.85	3.4
9	A.I.Green	Geis School of Medicine at Darmouth, USA	29	2499	86.17	20	2	6.90	3.4
10	S.Pollak	The Zucker Hillside Hospital, USA	24	1955	81.46	18	3	12.50	3.2

TP= Total publications; TC= Total citations; CPP= Citations per paper; HI= H-Index; ICP: International Collaboration papers; RCI: Relative Citation Index.

and 135387 citations, accounting for 51.67% share in global publications.

The journal which published the maximum number of articles was Journal of Clinical Psychopharmacology (351 papers), followed by Journal of Clinical Psychiatry (282 papers), American Journal of Psychiatry (255 papers. In terms of CPP, Archives of General Psychiatry (192.91) had highest CPP, followed by Schizophrenia Bulletin (103.28). In terms of total citations for clozapine publications papers published in American Journal of Psychiatry (17705 citations) received the maximum citations followed by Journal of Clinical Psychiatry (14772 citations) (Table 8).

High-Cited Papers

Out of all the publications on clozapine, 391 papers (5.28%) received 100 to 3584 CPP (assumed as high-cited) and together received 77722 citations, averaging a CPP of 198.78. Of the 391 high-cited papers, 294 are in citation range 100-200, 58 papers were in citation range 201-300, 18 papers were in citation range of 302-400, 9 papers were in the citation range of 432-500, 8 papers were in the citation range of 556-928 and 4 papers were cited 1025 to 3584 times.

Among 391 high-cited papers (comprising of 365 articles, 37 reviews, 10 letters, 8 conference papers and 1 editorial), 177 involved the participation of authors from single-institution (zero collaboration) and the rest 222 involved participation of authors from 2 or more organizations (168 national collaborative and 46 international collaborative). Among 391 high-cited papers, authors from USA contributed the largest number of papers (228 papers), followed by authors fromU.K. (35 papers), Germany (23 papers), Canada (17 papers), Sweden (16 papers), Switzerland (15 papers), Denmark and France (13 papers each), Australia (12 papers), Italy (11 papers), Finland and Netherlands (9 papers each), Israel and Taiwan (8 papers each), New Zealand (5 papers), China (4 papers), Japan, Spain and South Korea (3 papers each), Brazil and India (2 papers each), etc.

In terms of authors, H.Y. Meltzer (USA) contributed the largest number of high cited papers(34 papers), followed by J.A. Lieberman (USA)(25 papers), J.M. Kane (USA)(14 papers), R.W. Kerwin (U.K.) and A. Breier(USA)(11 papers each), D.C. Goff (USA)(10 papers), R.W. Buchanan (USA)(9 papers), R.J. Baldessarini (USA), D. Pickar (USA) and W.W. Fleischhacker (Austria)(7 papers each), J.P. Lindermayer (USA), A.I. Green (USA) and S. Pollak (USA)(6 papers each), A.Z. Safferman

Table 8:Profile of Top 20 journals publishing on "Clozapine".

Sl. No	Name of the Journal	TP	TC	CPP	HCP
1	Journal of Clinical Psychopharmacology	351	8610	24.53	20
2	Journal of Clinical Psychiatry	282	14772	52.38	45
3	American Journal of Psychiatry	255	17705	69.43	53
4	Psychopharmacology	204	9349	45.83	21
5	Schizophrenia Research	194	5455	28.12	10
6	Australian and New Zealand Journal of Psychiatry	120	1535	12.79	1
7	British Journal of Psychiatry	118	5219	44.23	18
8	Progress in Neuro Psychopharmacology and Biological Psychiatry	103	2271	22.05	
9	Neuropsychopharmacology	95	5777	60.81	15
10	Pharmacopsychiatry	92	2134	23.20	1
11	European Journal of Pharmacology	87	3210	36.90	6
12	Biological Psychiatry	86	5301	61.64	16
13	Journal of Psychopharmacology	85	1700	20.00	1
14	International Clinical Psychopharmacology	81	1899	23.44	1
15	Acta Psychiatrica Scandinavia	80	3023	37.79	8
16	Canadian Journal of Psychiatry	73	1239	16.97	1
17	Clinical Neuropharmacology	70	1844	26.34	2
18	European Neuropsychopharmacology	68	1607	23.63	2
19	Psychiatry Research	67	1301	19.42	2
20	Encephale	61	333	5.46	

TP= Total publications; TC= Total citations; CPP= Citations per paper; HCP: High cited papers.

(USA), J.H. Friedman (USA), J. Munro (U.K.) and D. Taylor (USA)(5 papers), F.R. Frankenburg (USA), O. Freudenrereich (USA) and J. Nielson (Denmark)(4 papers each), etc.

In terms of the journals, out of the 391 high-cited papers, *American Journal of Psychiatry* published the largest number of papers (53 papers), followed by *Journal of Clinical Psychiatry* (45 papers), *Psychopharmacology* (21 papers), *Journal of Clinical Psychopharmacology* (20 papers), *British Journal of Psychiatry* (18 papers), *Biological Psychiatry* (16 papers), *Neuropsychopharmacology* (15 papers), *Archives of General Psychiatry* and *The Lancet* (11 papers each), *Journal of Pharmacology and Experimental Therapeutics*, *Schizophrenia Research* and *Schizophrenia Bulletin* (10 papers each), *Acta Psychiatrica Scandinavica* (8 papers), *Therapeutic Drug Monitoring* (7 papers), *European Journal of Pharmacology* and *New England Journal of Medicine* (6 papers papers), *Brain Research* and *Neuro Reports* (5 papers each), *International Journal of Neuropsychopharmacology* and *Molecular Psychiatry* (4 papers each), *British Journal of Clinical Pharmacology, Hospital and Community Psychiatry, Neuroscience Letters* and *Movement Disorders* (3 papers each), *Clinical Neuropharmacology, Drug Safety, European Journal of Clinical Pharmacology, European Neuropsychopharmacology, Neuroscience, Psychiatry Research, Psychiatry Services, Psychopharmacology Bulletin, Synapse and Therapeutic Drug Monitoring* (2 papers each), etc.

DISCUSSION

The present bibliometric analysis suggests that over the last half a century, there is gradual increase in the number of publications on clozapine. When we compare the number of publications on clozapine between 1975 to 1987 and that of 1988 to 2000, it can be said that the number of publications on clozapine increased rapidly during this period. This can be understood from the perspective of history of clozapine. The Finnish epidemic about neutropenia associated with clozapine emerged in the year 1975 and in next couple of years the use of clozapine declined, till the famous trial by Kane *et al.*,[3] which led to resurgence of clozapine. Over the next 12 years, the research interest in clozapine increased and this is reflected by increase in the number of publications between the periods of 1988-2000. However, from 2001-2021, there is relative stability in the number of publications on clozapine. This stable number of publications can be understood from different perspectives. First, despite emergence in a number of newer antipsychotics, the interest in clozapine has not declined. The interest of researchers and clinicians on clozapine has persisted because of its superior efficacy/effectiveness of clozapine in patients with TRS. Second, this flattening of curve in terms of number of publications on clozapine, can be understood as the sustained effort of different group of researchers in this area, who have tried to increase the awareness of the clinicians who are scared to use clozapine. Additionally, the sustained number of publications can also be understood as an effort to increase

the awareness of clinicians about the safety of clozapine, despite its various side effects. The previous bibliometric study on clozapine had also noted the flat curve with respect to number of publications on clozapine over the years.[13]

When one examines the funded research, only one-sixth (16.07%) of the publications on clozapine are based on funded research. Considering that we are talking about a psychopharmacological agent, only one-sixth of the research on the same being based on funding suggests that, it is the interest of the researchers and clinicians in the molecule, which has led to the sustained research on clozapine, rather than the pharmaceutical industry.

In terms of type of publications, slightly more than two-third (68.33%) of the publications appeared as articles. Further analysis revealed that out of the 7399 global publications, 2080 publications were based on controlled studies, 370 were retrospective studies, 334 were based on comparative studies, 317 were clinical trials, and 254 were randomized controlled trials. In terms of various subjects, 2581 publications were clinical studies, 1065 publications focused on treatment outcome, 632 focused on side effects, 253 on risk factors, 250 focused on pathophysiology and 159 focused on genetics. This distribution shows that majority of the publications on clozapine are in the form of original research on various aspects of clozapine, varying from its side effect profile, comparison with other medications, and augmentation of clozapine with other molecules or somatic treatment strategies. The sustained interest in these forms of studies can be understood from various perspectives. First, considering the efficacy/effectiveness of clozapine in patients with TRS, researchers have tried to evaluate its efficacy/effectiveness in patients with first episode psychosis, so as to improve the long-term outcome of schizophrenia.[14,15] Second, it is estimated that about one-third of patients with TRS do not respond to clozapine.[16] Hence, there is a need to evaluate other psychopharmacological agents or somatic treatments for augmentation of clozapine. Accordingly a significant number of studies and reviews have focused on augmentation of clozapine.[17] Third, considering the fact that patients with TRS are a specific subgroup of schizophrenia, researchers have tried to evaluate the neurobiological underpinning of TRS and also the factors which predict the response or non-response to clozapine.[18] This has led to sustained research attention on clozapine. Fourth reason for sustained interest in clozapine has been its side-effect profile. Over the years it has been realized that, it is not only neutropenia, but some other side effects of clozapine (such as myocarditis, cardiomyopathy, seizures, constipation, hypersalivation) require attention to improve the tolerability of the molecule.[19] Hence, many efforts have been made to evaluate different agents and strategies to manage these side effects.

In terms of country wise distribution of publications on clozapine, maximum number of publications emerged from USA, followed by UK, Germany, Canada, Australia and Italy. Together, authors from top 10 countries contributed to 72.81% of total publications and 90.7% share of citations related to clozapine. This research profile on clozapine is understandable, considering the fact that majority of the psychiatric research emerges from the developed countries.[20] Considering the fact that there are pharmacogenomic and pharmacokinetic differences in response to clozapine,[21] this research profile is cause of concern, as this suggests that majority of the world population that resides in developing countries is under-represented in clozapine research.

The present analysis suggests that about one-third of the publications on clozapine are not targeted at patients with schizophrenia and rather focus on its role in the management of schizoaffective disorders, Parkinson's Disease, Bipolar Disorder, Suicidal Behaviour, Obsessive Compulsive Disorder, Personality disorders and other conditions. These findings reflect the broadening of the indications of clozapine for management of various psychiatric disorders, especially, the conditions which are difficult to manage. The focus on obsessive compulsive disorder could be due to the fact that clozapine is associated with high incidence of treatment emergent obsessive-compulsive disorder.[22]

In terms of organizations with maximum productivity on clozapine, out of the top 50 organizations, 20 were from USA, 4 each from Australia and Germany, 2 each from Canada, China, India, Israel, Netherlands, Spain and U.K. and 1 each from Brazil, Denmark, Finland, Italy, Singapore, Sweden, Switzerland and Turkey. Among the top 50 authors, again more than 40% were from USA, followed by 5 each from Canada and U.K., 3 each from Australia and Netherlands. The most productive authors were H.Y. Meltzer, followed by J. A. Lieberman, A. Weizman, G. Ramington and D. Siskind. In terms of most impactful authors, R.W. Kerwin topped the list, and he was followed by J.P. Lindermayer, A. Breier and J.A. Lieberman. This country and author profile again reflects the concentration of clozapine research in developed countries. The Sandoz International GmbH, Switzerland topping the list of clozapine research can be understood by the fact that this organization is was initially involved in manufacturing, research and marketing of clozapine.[1]

Among the most productive journals with respect to publications on clozapine was Journal of Clinical Psychopharmacology (351 papers), followed by Journal of Clinical Psychiatry (282 papers), American Journal of Psychiatry (255 papers), Psychopharmacology (204 papers), Schizophrenia Research (194 papers), Australian and New Zealand Journal of Psychiatry (120 papers), British Journal of Psychiatry (120 papers), Progress in Neuro Psychopharmacology and Biological Psychiatry (103 papers), Neuropsychopharmacology (95 papers) and Pharmacopsychiatry (92 papers). All these journals are based in USA and European countries, and most of them focus on psychopharmacology. However, papers published in Archives of General Psychiatry, Schizophrenia Bulletin,

Journal of Pharmacology and Experimental Therapeutics, American Journal of Psychiatry, The Lancet, Biological Psychiatry, Neuropsychopharmacology, Journal of Clinical Psychiatry, Psychopharmacology and International Journal of Neuropsychopharmacologyreceived higher CPP. This profile possibly suggests that research published in journals with high impact factor has more potential for being cited.

The present analysis has certain limitations. Although we used Scopus database to identify the clozapine publications that is much broader than the PubMed, it can still be aid to be narrower than Google Scholar. The analysis was also not based on Web of Science, which is considered to be broader than Scopus. It is important to understand that the most cited articles could be influenced by the time since publication, as this would have more chance to be cited over the period. The numbers of citations counted also were limited to Scopus database, which again is narrower than the Google Scholar. We did not specifically assess the focus of various studies, as this was not possible with the available logics in the Scopus databases.

CONCLUSION

To conclude, the present bibliometric analysis shows that there was sudden increase in the number of publications on clozapine after 1989, for a decade or so, after which there is flattening in the number of publications on clozapine. Most of the clozapine research emerges from developed countries, and majority of the publications are published in journals focusing on psychopharmacology. However, the research published in high impact factor journals is more cited. Considering the findings of the present analysis, it can be said that there is a need to improve the number of publications on clozapine from the developing countries.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Crilly J. The history of clozapine and its emergence in the US market: A Review and Analysis. Hist Psychiatry. 2007 Mar;18(1):39-60. doi: 10.1177/0957154X07070335, PMID 17580753.
2. Idänpään-Heikkilä J, Alhava E, Olkinuora M, Palva I. Letter: Clozapine and Agranulocytosis. Lancet. 1975;2(7935):611. doi: 10.1016/s0140-6736(75)90206-8, PMID 51442.
3. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A Double-blind Comparison with Chlorpromazine. Arch Gen Psychiatry. 1988 Sep;45(9):789-96. doi: 10.1001/archpsyc.1988.01800330013001, PMID 3046553.
4. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML, *et al*. Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry. 2017 Mar 1;174(3):216-29. doi: 10.1176/appi.ajp.2016.16050503, PMID 27919182.
5. Grover S, Hazari N, Chakrabarti S, Avasthi A. Delay in initiation of clozapine: A Retrospective Study from A Tertiary Care Hospital in North India. Psychiatry Res. 2015 Mar 30;226(1):181-5. doi: 10.1016/j.psychres.2014.12.046, PMID 25619433.
6. Siskind D, Sharma M, Pawar M, Pearson E, Wagner E, Warren N, *et al*. Clozapine levels as a predictor for therapeutic response: A Systematic Review and Meta-analysis. Acta Psychiatr Scand. 2021 Nov;144(5):422-32. doi: 10.1111/acps.13361, PMID 34374073.
7. Siskind DJ, Lee M, Ravindran A, Zhang Q, Ma E, Motamarri B, *et al*. Augmentation strategies for clozapine refractory schizophrenia: A Systematic Review and Meta-analysis. Aust N Z J Psychiatry. 2018 Aug;52(8):751-67. doi: 10.1177/0004867418772351, PMID 29732913.
8. Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: Systematic Review and Meta-analysis. Br J Psychiatry. 2016 Nov;209(5):385-92. doi: 10.1192/bjp.bp.115.177261, PMID 27388573.
9. Siskind D, Siskind V, Kisely S. Clozapine response rates among people with treatment-resistant schizophrenia: Data from a Systematic Review and Meta-analysis. Can J Psychiatry. 2017 Nov;62(11):772-7. doi: 10.1177/0706743717718167, PMID 28655284.
10. Lally J, Tully J, Robertson D, Stubbs B, Gaughran F, MacCabe JH. Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: A systematic review and meta-analysis. Schizophr Res. 2016 Mar;171(1-3):215-24. doi: 10.1016/j.schres.2016.01.024, PMID 26827129.
11. Chen SY, Ravindran G, Zhang Q, Kisely S, Siskind D. Treatment strategies for clozapine-induced sialorrhea: A systematic review and meta-analysis. CNS Drugs. 2019 Mar;33(3):225-38. doi: 10.1007/s40263-019-00612-8, PMID 30758782.
12. Veerman SR, Schulte PF, Begemann MJ, Engelsbel F, de Haan L. Clozapine augmented with glutamate modulators in refractory schizophrenia: A review and meta analysis. Pharmacopsychiatry. 2014 Sep;47(6):185-94. doi: 10.1055/s-0034-1383656, PMID 25002291.
13. López-Muñoz F, Sanz-Fuentenebro J, Rubio G, García-García P, Álamo C. Quo vadis clozapine? A bibliometric study of 45 years of research in international context. Int J Mol Sci. 2015;16(9):23012-34. doi: 10.3390/ijms160923012.
14. Tang C, Subramaniam M, Ng BT, Abdin E, Poon LY, Verma SK. Clozapine use in first-episode psychosis: The Singapore early psychosis intervention programme (EPIP) perspective. J Clin Psychiatry. 2016 Nov;77(11):e1447-53-e1453. doi: 10.4088/JCP.15m10063, PMID 27736048.
15. Doyle R, Behan C, O'Keeffe D, Masterson S, Kinsella A, Kelly A, Sheridan A, Keating D, Hynes C, Madigan K, Lawlor E, Clarke M. Clozapine Use in a Cohort of First-Episode Psychosis. J Clin Psychopharmacol. 2017 Oct;37(5):512-517.
16. Meltzer HY. Treatment of the neuroleptic-nonresponsive schizophrenic patient. Schizophr Bull. 1992;18(3):515-42. doi: 10.1093/schbul/18.3.515, PMID 1357741.
17. Grover S, Sahoo S. Treatment of clozapine nonresponders. Curr Treat Options Psychiatry. 2019;6(1):32-63. doi: 10.1007/s40501-019-0166-4.
18. Suzuki T, Uchida H, Watanabe K, Kashima H. Factors associated with response to clozapine in schizophrenia: A review. Psychopharmacol Bull. 2011;44(1):32-60. PMID 22506438.
19. Miller DD. Review and management of clozapine side effects. J Clin Psychiatry. 2000;61;Suppl 8:14-7; discussion 18. PMID 10811238.
20. Zhang J, Chen X, Gao X, Yang H, Zhen Z, Li Q, *et al*. Worldwide research productivity in the field of psychiatry. Int J Ment Health Syst. 2017;11:20. doi: 10.1186/s13033-017-0127-5, PMID 28289438.
21. de Leon J, Schoretsanitis G, Smith RL, Molden E, Solismaa A, Seppälä N, *et al*. An international adult guideline for making clozapine titration safer by using six ancestry-based personalized dosing titrations, CRP, and clozapine levels. Pharmacopsychiatry. 2022 Mar;55(2):73-86. doi: 10.1055/a-1625-6388, PMID 34911124.
22. Schirmbeck F, Zink M. Clozapine-induced obsessive-compulsive symptoms in schizophrenia: A critical review. Curr Neuropharmacol. 2012 Mar;10(1):88-95. doi: 10.2174/157015912799362724, PMID 22942882.

Cite this article: Grover S, Gupta BM, Ahmed KKM, Singh Y. Clozapine: A Scientific Analysis of Global Publications during 1970-2021. Int. J. Pharm. Investigation. 2023;13(1):14-21.