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RESEARCH ARTICLE

Bibliometric Analysis of Academic Articles on Epidemic of Prescription Opioid Deaths, 1988-2017

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ABSTRACT

Purpose: The current study assesses how academic medical journals reflected the prescription opioid death crisis. The principal aim was to answer the question: How long did it take to reach definite bibliometric acknowledgment of deaths from opioid epidemic?

Methods: Death-related bibliometric indices were determined for opioids associated with increased mortality. The main of them is the percentage of articles on an individual opioid associated with death among all PubMed articles on that opioid. The bibliometric indices were followed for six 5-year periods, from 1988 to 2017. The time course for each of the indices were compared for two groups of opioids: 1) Those used for the treatment of chronic pain ("root cause of the epidemic") – such as oxycodone, hydrocodone, and tramadol, and 2) Those which were always associated with the death due to addiction -- heroin and methadone. The difference in death-related bibliometric indices between these two groups of opioids was used as an indicator of changes in presentation of opioid deaths.

Results: The articles reporting death associated with oxycodone, tramadol, or hydrocodone became noticeable during 2003-2007, ten years after the beginning of epidemic (1993-1997). It was only in 2013-2017 mortality associated with these opioids were presented at the levels close to those of heroin or methadone. Only during 2013-2017 (twenty years after the beginning of epidemic) was death associated with oxycodone presented in journals as openly (in the article's titles) as that associated with heroin, or methadone.

Conclusion: The danger of death from treatment of chronic pain with opioids was not properly appreciated for almost twenty years.

Introduction

The dramatic rise in the number of deaths involving opioid overdoses[1] became clear in the early 1990s. Unprecedented demand for management of chronic nonmalignant pain and a profound increase in the number of prescriptions for opioid analgesics for this purpose have been identified as "a root cause of the epidemic of prescription opioid abuse and deaths".[2-5] Research publications on successful long-term treatment of chronic pain with opioids appeared in the 1980s; during the 1960s-1970s consensus was that treatment of chronic pain patients with opioids was "unwise".[6] In the first half of 80s, several research studies on successful long-term treatment of chronic pain with opioid analgesics were published.[7-9] They represented case series reports, but became very popular. The last of them[9] had more than 5 hundred citations. The first studies describing the marked increase in prescription opioid deaths appeared in 2005-2006, but general recognition of the role of opioids prescribed for chronic pain in deaths from opioid epidemic came much later.

The current study assesses how academic medical journals reflected the opioid crisis using specific bibliometric indices. The principal aim of the current study was to answer the question: How long did it take to reach definite bibliometric acknowledgement of deaths from the opioid epidemic? For this purpose it was necessary to determine the times of marked increases in reporting of opioid deaths in academic journals. Opioids commonly used for the treatment of chronic pain (oxycodone, hydrocodone, and tramadol) were compared to opioids traditionally associated with death due to addiction (heroin and methadone). The difference in death-related bibliometric indices between these two groups of opioids was used as an indicator of changes in the presentation of opioid deaths in academic publications.

Methods

General approach

Publication-based academic interest related to a specific medicobiological issue can be analyzed using the databases of medicobiological publications. The PubMed database of the US National Library of Medicine is the largest authoritative source of such information. It comprises more than 34 million citations for biomedical literature that are well classified and, most importantly, has a controlled and extremely reliable vocabulary for article indexing (MeSH [Medical Subject Headings] terms). Various bibliometric indices have been developed mainly on the basis of this database.[10-13]The following MeSH terms related to opioid deaths were included in our searches: death-related terms -- "Death", "Fatality", and "Mortality"; individual opioids -- "Oxycodone", "Tramadol", "Hydrocodone", etc; and opioid drugs as a group—"Analgesics, Opioid". Articles related to these terms were counted using the PubMed Web site (http://www.ncbi.nlm.nih.gov/PubMed). An individual opioid name was entered in the search box with the terms "Death OR Mortality OR Fatality," and the number of articles was determined for each topic.

According to the US Center for Disease and Prevention, a sustained rise of unintentional opioid mortality (above 40 -- yearly rate per 10 million)[14,15] was observed after 1992. This rise was used to determine the time intervals for grouping of the data on bibliometric indices: one 5-year group (1988-1992) was chosen before and five others (1993-1997, 2013-2017) after it.

An opioid was included in the list for assessment if the count of articles (when an opioid's name combined with the mortality-related terms and the term "Chronic Pain") exceeded 10 during 1988-2017. The selected drugs included two types of opioids: those used for the treatment of chronic pain (oxycodone, hydrocodone, tramadol, and codeine); – and those traditionally associated with addiction – heroin, which is not a legal drug in the US, and methadone, which is commonly applied in opioid use disorder. Differences in death-related bibliometric indices of these two groups of opioids were used to characterize the presentation of deaths when it is related to opioids used for the treatment of pain.

Bibliometric indices

The following bibliometric indices were used: total number of articles, popularity index **(PI)**, index of change **(IC)**, and index of exposure in titles **(IET)**. **PI** is the percentage of articles on an individual opioid associated with death among all PubMed articles on that opioid published over the same 5 years.[12] **PI** includes all types of articles in all journals covered by PubMed. There is a constant growth in number of PubMed drug-related articles in all medicobiological areas. On average, growth is in the range of 20-30% per 5-year period, but it varies in different areas; the **PI** allows the measurement of comparative popularity of a topic among the authors of articles.

The **Index of Change (IC)** reflects the change in the number of publications on a topic during a 5-year period compared to a previous 5-year period.[12] It is calculated as the percentage change

in the number of articles on a particular topic between two periods: the difference between these periods is divided by the original number and multiplied by 100. The **IC** represents the degree of change in the authors' interest in that topic irrespective of changes in the related area.

Placement of a specific term in an article's title is an indication of the importance of a term-related problem.[16] To analyze the degree of openness with which opioid-related death was shown, we used a specific index **-- Index of Exposure in Titles (IET).** IET is the percentage of articles on an individual opioid with the terms "Death", "Mortality", or" Fatality" in the article's title among all articles on this opioid associated (by PubMed) with the mortality-related terms. The name of an opioid was used in combination with death-in-title terms; for example, "Oxycodone AND (Death[title] OR Mortality[title] OR Fatality[title])". IET and PI were regarded as undetectable when the number of articles associated with death did not reach the threshold of 10 during a 5-year period.

Editorials on prescription opioid deaths

Editorials (articles solicited by an editorial board to provide a perspective on an article published in a journal) on prescription opioid deaths reflect the problem's importance as assessed by that journal's board. For initial searches of the PubMed website, the following terms were placed in the search box: "Analgesics, Opioid AND (Death OR Mortality OR Fatality)"; and the filters "Editorial" and "Humans" were activated. In addition to the electronic searches for editorials, related articles were also collected manually from the lists of references in the literature on the opioid epidemic. The publications identified were narrowed down to those clearly marked as editorials; editorials with no authors listed were excluded and the publications were counted for each of the 5-year periods identified above. The number of citations an editorial elicited was counted using the Web of Science service. The total number of citations, from the year of publication of an editorial to the end of 2017, was determined.

Results

Table 1 presents data on bibliometric indices for individual opioids markedly associated with mortality. The opioids are presented from the highest to lowest number of articles associated with the mortality-related terms. Heroin and methadone had the highest number of such articles during all time intervals. Because of constant growth in the number of academic publications on opioids in general, the popularity index (PI) – the percentage of articles on an opioid associated with death among all PubMed articles on that opioid – allows us to compare situations during different time intervals. Table 1 shows that the PI of heroin varied from 8.9 (1988-1992) to 15.8 (2013-2017) over time; in half of the time periods this index was close to 10. With methadone, the PI varied from 6.9 (1988-1992) to 13.0 (2013-2017), but in three of six periods its value was also close to 10. The PI of opioids most commonly used for the treatment of chronic pain – oxycodone, tramadol, and hydrocodone – had a PI pattern very different from those of heroin or methadone. First of all, during the three initial time intervals there were almost no articles associated with death, making the PI impossible to calculate. With oxycodone and tramadol, it became possible to determine the PI only starting with the 2003-2007 interval -- 6.9 and 4.0, respectively. Later, these PIs increased, but only to 9.1 and 5.7 by 2013-2017. Fentanyl had a detectable PI, even during the three initial time intervals – 2.5 (1988-1992), 1.7 (1993-1997), and 3.1 (1998-2002), and it increased to 8.4 in 2013-2017. The PI value of codeine varied from 4.6 (1993-1997) to 7.7 (2008-2012).

Table 1. Biblimetric indices for articles on opioids with markedly increased level of mortality

Opioid	Years	Number of All Articles[1]	Articles Associated with Term "Death"[2]			Articles with Term "Death" in Title	
			Number	PI[3]	IC[4]	Number	IET[5]
Heroin[6]	1988-1992	846	75	**8.9**	-	10	**13.3**
	1993-1997	1,069	111	**10.4**	48	19	**17.1**
	1998-2002	1,352	173	**12.8**	56	29	**16.8**
	2003-2007	1,847	201	**10.9**	16	30	**14.9**
	2008-2012	1,893	201	**10.6**	0	44	**21.9**
	2013-2017	2,157	340	**15.8**	68	60	**17.6**
Methadone	1988-1992	582	40	**6.9**	-	8	-[7]
	1993-1997	868	55	**6.3**	41	8	-
	1998-2002	1,146	107	**9.7**	94	19	**17.8**
	2003-2007	1,602	154	**9.7**	46	19	**12.2**
	2008-2012	1,933	203	**10.3**	28	44	**21.7**
	2013-2017	2,107	274	**13.0**	36	43	**15.9**
Fentanyl	1988-1992	1,733	43	**2.5**	-	2	-
	1993-1997	2,121	36	**1.7**	(-16)	1	-
	1998-2002	2,105	65	**3.1**	80	0	-
	2003-2007	2,387	92	**3.8**	42	2	-
	2008-2012	2,402	130	**5.4**	41	2	-
	2013-2017	2,574	217	**8.4**	67	20	**9.2**
Codeine	1988-1992	301	9	-[7]	-	0	-
	1993-1997	454	21	**4.6**	75	2	-
	1998-2002	509	25	**4.9**	19	3	-
	2003-2007	680	43	**6.3**	72	2	-
	2008-2012	952	73	**7.7**	70	4	-
	2013-2017	1,257	95	**7.6**	30	14	**14.7**
Oxycodone	1988-1992	44	0	-	-	0	-
	1993-1997	72	1	-	-	0	-
	1998-2002	128	2	-	-	0	-
	2003-2007	366	26	**6.9**	-	0	-
	2008-2012	689	53	**7.6**	104	4	-
	2013-2017	943	87	**9.1**	64	14	**16.1**
Tramadol	1988-1992	49	0	-	-	0	-
	1993-1997	139	1	-	-	0	-
	1998-2002	317	5	-	-	2	-
	2003-2007	605	14	**4.0**	-	3	-
	2008-2012	795	34	**4.3**	42	3	-
	2013-2017	906	52	**5.7**	53	2	-
Hydrocodone	1988-1992	10	0	-	-	0	-
	1993-1997	26	0	-	-	0	-
	1998-2002	67	2	-	-	0	-
	2003-2007	123	7	-	-	1	-
	2008-2012	189	25	**13.2**	-	3	-
	2013-2017	292	29	**9.9**	16	4	-

Footnotes for Table 1

[1]PubMed articles with the "Abstract", and "Humans" filters activated.

[2]Aricles associated (by the PubMed) with the following PubMed MeSH terms "Death", or "Mortality", or "Fatality".

[3]PI – Populatity Index, the percentage of individual opioid articles associated with the term "Death" among all PubMed articles on this opioid (bold).

[4]IC – Index of Change, the percentage change in the number of articles during a 5-year period compared with the previous similar period.

[5]IET – Index of Exposure in Titles, the percentage of articles on an individual opioid with term "Death"[2] in the article's title among all articles associated by the PubMed with this term (bold).

[6]The opioids are presented in the order of highest mortality during 2013-2017.

[7] IET or PI was regarded as undetectable when the number of articles associated with death did not reach the threshold of 10 during a 5-year period.

The last column of Table 1 presents data related to articles on individual opioids with the term "Death", "Mortality", or "Fatality" in the title. This allows determination of the Index of Exposure in Titles (IET), the percentage of articles on an individual opioid with mortality-related terms in the title among all articles associated (by PubMed search algorithm) with these terms. This index has a wide range with heroin and methadone at one extreme, and the opioids commonly used for the treatment of chronic pain at the other. The IETs of heroin and methadone, although somewhat variable, were high and remained mostly stable during the last four or five 5-year periods: from 16.8 to 21.9 with heroin and from 12.2 to 21.7 with methadone. With all other opioids in this table, there were too few articles with mortality-related terms in the title to calculate IET, except for the last of the six 5-year periods (2013-2017). With oxycodone, codeine, and fentanyl the IET was 16.1, 14.7, and 9.2, respectively. For tramadol and hydrocodone, IET was below the threshold level of articles associated with death to calculate it in any of the time periods.

Table 2 presents editorials[17-28] on prescription opioid deaths and the citation responses they elicited. During the first three 5-year periods of the opioid epidemic (1993-1997, 1998-2002, and 2003-2007) there were no authored editorials on this topic (except one article in 2003[17] with a zero-citation impact). Editorials began to be published only in 2008-2012, and totaled six, only three of which had notable citation impacts. There were another six editorials in 2013-2017, but their citation impact was insignificant.

Discussions

The principal aim of the current study was to answer the following question: How long did prescription opioid deaths take to achieve bibliometric acknowledgement? In other words, when did academic publications properly reflect the reality of this epidemic? This question was answered by comparing opioids commonly used for the treatment of chronic pain (oxycodone, hydrocodone, and tramadol), to opioids traditionally associated with death due to addiction (heroin and methadone). Death-related bibliometric indices were used to assess the difference between these two groups. They were determined at two levels: 1) a basic level, i.e., when an article on an opioid was associated (by PubMed) with the term "Death" (or "Mortality", or "Fatality") – reflected mostly by PI; and 2) a more specific level, when the term "Death" was present in the article's title – reflected by IET. The difference between these two levels is the difference between simple reporting of an event and explicitly emphasizing its importance. Since the beginning of the epidemic of prescription opioids deaths (1993-1997) there was a profound difference between heroin (or methadone), on one hand, and opioids used for the treatment of chronic pain (oxycodone, tramadol, or hydrocodone), on the other, with respect to both the PI and IET indices. The heroin or methadone PI was never far from 15 over the periods studied (Table 1). However, with oxycodone, tramadol, and hydrocodone these indices were not even calculable for several of the initial 5-year periods due to the absence of appropriate academic publications. With oxycodone such publications appeared in 2003-2007, when PI was determined to be 6.9. Then it gradually increased to 9.1 (2013-2017) – still lower than the PI of heroin or methadone. A similar situation was seen with tramadol and hydrocodone (Table 1). IET was detectable with oxycodone only during the last time interval, 2013-2017. However, it was immediately rather high –16.1, almost the same level as those of heroin and methadone -- 17.6 and 15.9, respectively (Table 1).

The opioids listed in Table 1 also include codeine and fentanyl. The initial PIs of codeine are closer to those of methadone than oxycodone. The number of articles addressing death related to fentanyl was much higher than expected, especially during 1988-1992 – 43 articles (Table 1). This is due to the very large number of all articles related to fentanyl; for example, in 1988-1992 the number of all fentanyl articles was 1,733, far exceeding any of the other opioids analyzed. This can be explained by the very wide use of fentanyl not only for the treatment of pain, but also for anesthesia induction and maintenance. The number of deaths associated with fentanyl, especially in the early 5-year periods, probably also reflected death related to anesthesia and surgery.

Editorials in academic journals also showed a very delayed response to deaths from the prescription opioid epidemic (Table 2). During the first three 5-year periods (1993-1997, 1998-2002, and 2003-2007) there was only one editorial (in 2003),[17] and it had zero citations. Although there were six editorials in 2008-2012 and another six in 2013-2017, overall, they had little citation impact (nine of the twelve had only 2-5 citations each). The large number of citations for one of the editorials (published in *New England Journal of Medicine* in 2010[2], 499 citations) only emphasized

the rarity of citations for the other editorials. Thus, the citation impact of editorials on mortality from the prescription opioid epidemic, in toto, reflect little interest in these topics, especially during the first 10-15 years of the epidemic.

Thus the presented results on opioids used for chronic pain reveal an almost complete absence of death-related articles for the initial two 5-year periods of the epidemic (1993-1997 and 1998-2002), followed by a very slow increase in frequency of death-related publications during the next two 5-year periods years (2003-2007 and 2008-2012). Only during the fifth 5-year period of the epidemic (2013-2017), were deaths associated with oxycodone presented in journals as openly as deaths associated with heroin or methadone.

Table 2. Editorials on prescription opioid deaths and citation responses they elicited

Years	Number of Editorials	Editorials and Citation			
		First Author	Journal	Year	Number of Citations*
1993-1997	0	--	--	--	--
1998-2002	0	--	--	--	--
2003-2007	1	Barbulo JP[17]	*Journal of Managed Care Pharmacy*	2003	0
2008-2012	6	McLellan AT[18]	*JAMA*	2008	61
		Rathmell JP[19]	*Anesthesiology*	2009	6
		McLellan AT[20]	*Annals of Internal Medicine*	2010	47
		Okie S[2]	*New England Journal of Medicine*	2010	499#
		Fishman SM[21]	*Pain Medicine*	2011	2
		Dhalla IA[22]	*British Medical Journal*	2012	2
2013-2017	6	Lipman AG[23]	*Journal of Pain & Palliative Care Pharmacotherapy*	2012	4
		Katz MH[24]	*JAMA Internal Medicine*	2013	4
		Berge KH[25]	*Mayo Clinic Proceedings*	2014	5
		Middleton J[26]	*British Medical Journal*	2016	12
		Burke DS[27]	*Science*	2016	4
		Mahan KT[28]	*Journal of Foot and Ankle Surgery*	2017	4

Footnotes for Table 2

*Citations during the period ending in 2017

#Actually a "perspective" type article by a NEJM writer

This study presents bibliometric data on opioid-related mortality for six 5-year periods, from 1988 to 2017. By 2013-2017 the prescription of opioids for chronic pain was identified as a root cause of the opioid death epidemic.[2-5] However, despite the subsequent reduction in opioid prescriptions, opioid-related mortality continues to grow.[29]

How does one explain the apparent delay in academic publications reflecting this epidemic? One reason may be the very nature of changes in the use of drugs over time, which is extremely slow. For example, the process by which a clearly less-effective class of drugs is supplanted by a more effective one (such as the use of sumatriptan instead of ergotamine for migraine) usually requires 10 -25 years.[30] Another explanation is the absence of real progress in the development of new analgesics effective in chronic pain, especially with respect to neuropathic pain.[31] The enormity of the number of deaths during the prescription opioid epidemic, not to mention the additional problems of opioid misuse and addiction, suggest that the slow academic response to deaths from opioid epidemic deserves special attention.

In conclusion, the reflection in academic journals of the epidemic of deaths associated with opioids used for chronic pain can be characterized as follows: Almost complete absence of mortality-related publications for the first ten years of the epidemic followed by a very slow increasing frequency of the publications for the next ten years. As a result, the danger of death from treatment of chronic pain with opioids was not properly appreciated for almost twenty years.

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