Methodological Reviews

Bibliometric Network Analysis on Rapid-Onset Opioids for Breakthrough Cancer Pain Treatment

Marco Cascella, MD, Federica Monaco, MD, Davide Nocerino, MD, Elisabetta Chinè, MD, Roberta Carpenedo, MD, Paola Picerno, MD, Laura Migliaccio, MD, Angela Armignacco, MD, Giulia Franceschini, MD, Sergio Coluccia, MStat, Piergiacomo Di Gennaro, MStat, Maura C Tracey, BSN, Cira A Forte, PSYD, Mariangela Tafuri, MStat, Anna Crispo, MStat, Francesco Cutugno, PhD, Alessandro Vittori, MD, Silvia Natoli, MD, PhD, and Arturo Cuomo, MD

Division of Anesthesia and Pain Medicine (M.C., F.M., D.N., M.C.T., C.A.F., A.C.), Istituto Nazionale Tumori, IRCCS Fondazione G, Pascale, 80100 Naples, Italy; Department of Electrical Engineering and Information Technologies (M.C., F.C.), Università di Napoli "Federico II", 80100 Napoli, Italy; Unit of Pain Therapy (E.C., R.C., S.N.), Polyclinic of Tor Vergata, Rome, Italy; Residency Programme of Anaesthesiology (P.P., L.M., A. A., G.F.), Intensive Care and Pain Therapy. University of Rome Tor Vergata, Italy; Epidemiology and Biostatistics Unit (S.C., P.D.G., M.T., A.C.), Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, 80100 Naples, Italy; Department of Anesthesia and Critical Care (A.V.), ARCO Roma, Ospedale Pediatrico Bambino Gesù IRCCS, Rome, Italy; Department of Clinical Science and Translational Medicine University of Rome (S.N.), Tor Vergata, Rome, Italy

Abstract

Background and Objectives. Proper breakthrough cancer pain (BTcP) management is of pivotal importance. Although rapid-acting, oral and nasal transmucosal, fentanyl formulations (rapid-onset opioids, ROOs) are licensed for BTcP treatment, not all guidelines recommend their use. Presumably, some research gaps need to be bridged to produce solid evidence. We present a bibliometric network analysis on ROOs for BTcP treatment.

Methods. Documents were retrieved from the Web of Science (WOS) online database. The string was "rapid onset opioids" or "transmucosal fentanyl" and "breakthrough cancer pain". Year of publication, journal metrics (impact factor and quartile), title, document type, topic, and clinical setting (in-patients, outpatients, and palliative care) were extracted. The software tool VOSviewer (version 1.6.17) was used to analyze the semantic network analyzes, bibliographic coupling, journals analysis, and research networks.

Results. 502 articles were found in WOS. A declining trend in published articles from 2014 to 2021 was observed. Approximately 50% of documents regard top quartile (Q1) journals. Most articles focused on ROOs efficacy, but abuse and misuse issues are poorly addressed. With respect to article type, we calculated 132 clinical investigations. The semantic network analysis found interconnections between the terms "breakthrough cancer pain," "opioids," and "cancers." The top co-cited article was published in 2000 and addressed pain assessment. The largest number of partnerships regarded the United States, Italy, and England.

Conclusion. In this research area, most articles are published in top-ranked journals. Nevertheless, paramount topics should be better addressed, and the implementation of research networks is needed. J Pain Symptom Manage 2022;000:e1−e10. ©

Key Words

Bibliometric analysis, breakthrough cancer pain, transmucosal fentanyl, rapid-onset opioids

Key Message

This study concerns a bibliometric network analysis on oral and nasal transmucosal fentanyl for breakthrough cancer pain treatment. It is a topic of paramount importance. Results can be

Address correspondence to: Marco Cascella, Division of Anesthesia and Pain Medicine, Istituto Nazionale Tumori, IRCCS Fondazione G, Pascale, 80100 Naples, Italy E-mail: m.cascella@istitutotumori.na.it

Accepted for publication: 27 January 2022.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2022.01.023

helpful for stimulating future studies, filling research gaps, and obtaining solid scientific evidence.

Introduction

Breakthrough cancer pain (BTcP) is a sudden exacerbation of pain despite adequate control with opioid therapy.[1] This type of pain is a frequent condition and can affect up to 70% of patients suffering from chronic pain of oncological nature.[2] Notably, because it is associated with negative outcomes for both patients and healthcare providers,[3] careful BTcP management is mandatory.[4,5]

Nevertheless, BTcP treatment is a great challenge and requires rescue doses of strong opioids. Several opioids are used for BTcP management. Among these, rapid-acting, oral and nasal transmucosal, fentanyl formulations (rapid-onset opioids, ROOs) are licensed for the treatment of BTcP. Nonetheless, Scientific Societies have not reached a consensus about the preferred strategy for managing this pain phenomenon. For example, the European Society for Medical Oncology (ESMO) guidelines strongly recommend the use of ROOs (level of evidence I, degree of recommendation A).[6] On the contrary, the WHO guidelines indicated that BTcP should always be relieved with rescue drugs based on clinical experience and patient need, and recommend immediate-release or slow-release morphine.[7] The European Association for Palliative Care (EAPC) guidelines indicated oral opioids as first-line treatment, although ROOs are suggested when a rapid onset and shorter duration of effect are needed. In these guidelines, the use of ROOs to treat preemptively (e.g., 30 minutes before the provoking procedure) predictable episodes of BTcP is not recommended.[8] Moreover, generic guidelines suggest oral opioids, whereas specific BTcP guidelines recommend ROOs. According to Davis et al.,[1] the different attitudes towards BTcP management "do not reflect research evidence but personal opinions." In a recent analysis, conducted on the unpredictable BTcP subtype, we identified four clusters according to pain intensity, the number of episodes/day, and the type of pain. Results showed that clinicians limit the use of ROOs in the treatment of the most severe forms of BTcP.[9]

Research plays a key role in providing evidence for deciding treatment options and, probably, some research gaps in this field need to be bridged. This bibliometric analysis is aimed at characterizing the developed research in the subject. It could provide useful findings for predicting the direction of future studies, implementing corrective measures, intensifying networks, and stimulating translational research processes.

Methods

Data Collection

The methodology refers to the strategy adopted in other bibliometric investigations.[10,11] The global literature about ROOs was scanned in the Web of Science (WOS) online database. The search terms and string applied to identify the closest matching articles included "rapid-onset opioids" or "transmucosal fentanyl," and "breakthrough cancer pain." No language restrictions were applied. All data were acquired on December 26, 2021. Data were exported as a Microsoft Excel (.xlsx) file.[12]

Research Methods

The information for the documents that met the requirements, including the year of publication, journal, journal's metrics (impact factor and quartile), title, document type, topics, clinical setting (in-patients, outpatients, and palliative care), and count of citations were extracted. For journal metrics, the source was Journal Citation Reports™ 2020 (Clarivate Analytics).

The trend in the annual number of documents was calculated with the joint-point analysis (Joinpoint Regression Program software, version 4.9.0.0) and the Dickey-Fuller test. The average annual percent change (APC) in publication rates synthetically explains the sign and intensity of the time variation. The model is based on linear segments connected at join points that represent the best fit of the observed data. These segments minimize the sum of the square of the differences between estimated and observed data. The joinpoint year is the point in time where the trend variation is estimated.

The literature analysis and knowledge visualization software tool VOSviewer (version 1.6.17) was used to analyze the following features:

- Co-occurrence of keywords. A co-occurrence network or semantic network analyzes potential relationships between terms (interconnection).[13]
- Co-citation. Also termed as bibliographic coupling, refers to the rate with which two documents are cited together by other documents.[14]
- Co-citation analysis for sources (journals).
- Co-authorship analysis (by countries). It expresses the collaborative efforts among institutions and countries.[15]
- Analysis of the most productive organizations and their collaborations.

Results

According to search strategies, a total of 502 articles on transmucosal fentanyl for the treatment of BTCP were published from 1989 to 2021, in WOS.

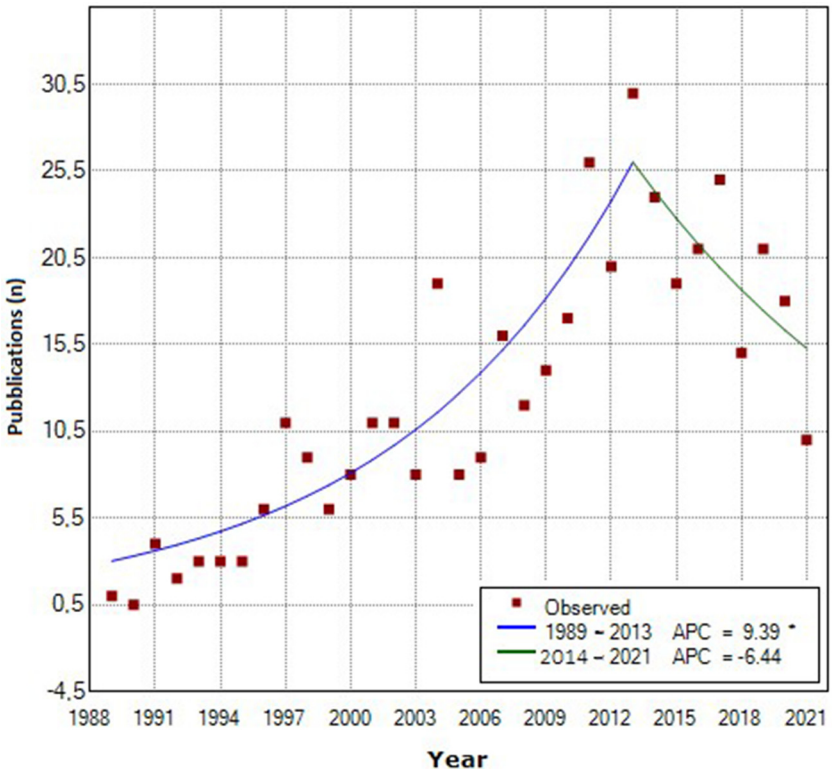

Fig. 1. Annual trend of the articles published on transmucosal fentanyl (Joint-point analysis). In the whole study period (1989–2021), a linear trend for the annual new publications series was observed (Dickey-Fuller test, $P = 0.73$). For the 1989–2021 trend, we found two segments with different slopes. In the 1989–2013 period, we calculated a significant increase in the annual percent change (APC) (APC = 9.39: 95% CI 6.8–12.0; $*P < 0.001$). Concerning the 2014-2021 period, the APC was not significant (APC = -6.44; $P = 0.088$).

Bibliometric Analysis of Publication Output

The trend in the annual number of documents on transmucosal fentanyl is shown in Fig. 1. A linearly increasing trend is almost visible during the last 32 years. However, a deflection of new documents from 2014 to 2021 was recorded, and the published articles decreased from 24 (in 2014) to 10 (in 2021). On WOS, the number of "articles" was 209/312 (67%) in the 1989–2013 period, and 129/190 (67.9%) in the 2014–2021 interval.

Table 1
Top 10 Most Productive Journals and Metrics

Journal	Impact Factor[a]	Best Quartile[a]	Articles (n)
Journal of Pain and Symptom Management	3.612	Q2	37
Anesthesiology	7.892	Q1	19
Drugs	9.546	Q1	17
Current Medical Research and Opinion	2.58	Q2	16
Anesthesia and Analgesia	5.178	Q1	12
Supportive Care in Cancer	3.603	Q2	12
Pain	6.961	Q1	11
Pain Medicine	3.75	Q2	10
Clinical Journal of Pain	3.442	Q2	8
European Journal of Pain	3.934	Q2	8

Legend.
[a]Source: Journal Citation Reports™ 2020.

Regarding journal metrics, the top 10 most productive journals are listed in Table 1.

The analysis of Quartile found that 46% of the articles were published in Q1 journals (Fig. 2).

Different types of studies were published. Among the whole set (n = 502), we calculated 97 narrative reviews, 67 observational studies, and 65 randomized clinical trials (RCTs). An amount of 73 documents were guidelines and recommendations (n = 22), preclinical investigations, commentaries, meeting abstracts, proceeding papers, early access papers, corrections, and notes (Fig. 3).

Most articles focused on efficacy (n = 282), clinical management (n = 238), administration routes (n = 244), and doses (n = 202; Fig. 4). With reference to setting, 32% of the documents focused on palliative care; 32% inpatients, and 36% outpatients.

Analysis of Author Cooperation Network

Bibliometric Analysis of the Keywords. The analysis concerned keywords provided by authors and occurred more than 5 times in the WOS core database. Of the 1,874 keywords, 155 met the threshold. The keywords that appeared most were BREAKTHROUGH PAIN

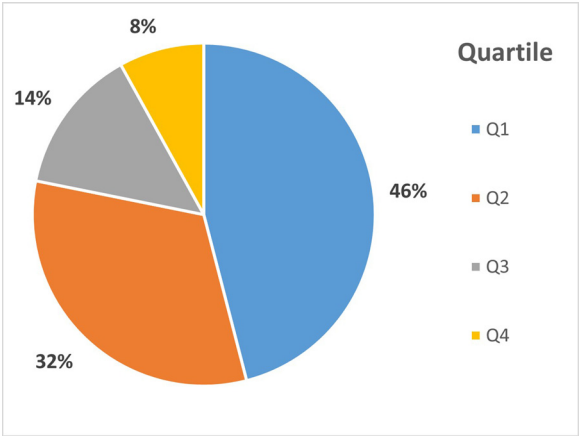

Fig. 2. Quartile analysis. For journals included in different categories, the best quartile was used.

(occurrence 152; total link strength 1126); OPIOIDS (127/780), and CANCERS (94/773) (Fig. 5).

Co-citation Analysis. A descriptive analysis of the top 10 co-cited articles [15–24] is reported in Table 2.

For the co-citation study, we used cited sources (journals) as a unit of analysis. The minimum number of citations of a source was 20. Thus, of 3,177 sources, 146 met the threshold. For each of 146 sources, the total strength of the co-citation links with other sources was calculated. The JOURNAL PAIN SYMPTOM MANAGEMENT obtained 1,403 citations and 142 links; PAIN 1,387 citations and 144 links; ANESTHESIOLOGY 1,023 citations and 143 links (Fig. 6).

Co-authorship Analysis (Countries). The minimum number of documents (threshold) per country was 5. Consequently, 19 countries met the threshold. The largest number of partnerships regarded the United States, Italy, and England. In the United States, 196 documents with 17 links were recorded, and in Italy, 86 documents and 13 links. In recent years, there has been an increase in publications from China, South Korea, and India. (Fig. 7)

The Most Productive Organizations and Their Collaborations. The analysis of affiliations (organizations) was conducted by considering the cut-off number of 5 as the minimum number of documents. Out of 901 organizations, 26 met the threshold. For each of these 26 organizations, the total strength of the citation links with other organizations was calculated. The organizations with the greatest total link strength were selected. LA MADDALENA CANCER CENTER (Italy) produced 35 documents and a total link strength of 719; The UNIVERSITY OF PALERMO (Italy) published 25 documents and 573 collaboration links; The UNIVERSITY of UTAH 13 documents and 244 links (Fig. 8).

Discussion

Although other bibliometric analyses have been conducted about opioids,[25] to our knowledge, this is the first analysis focused on the use of ROOs. In recent years, the trend analysis demonstrated a progressively lowered interest in the topic. In fact, since 2014, there has been a decline in the number of published documents. Nevertheless, the number of clinical articles remained unchanged. Probably this may reflect the need to better characterize the peculiarity of BTcP and its treatment. Indeed, there is still no consensus on the

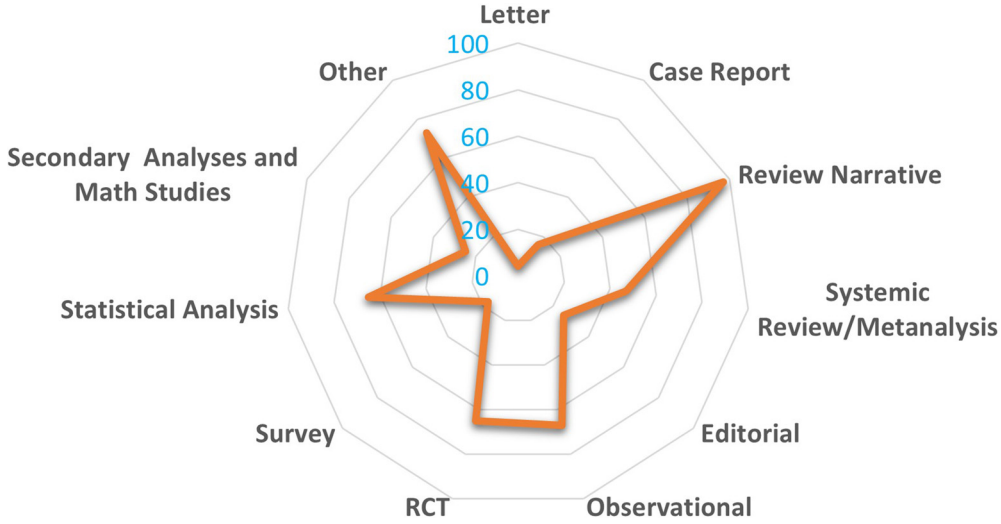

Fig. 3. Types of the study.

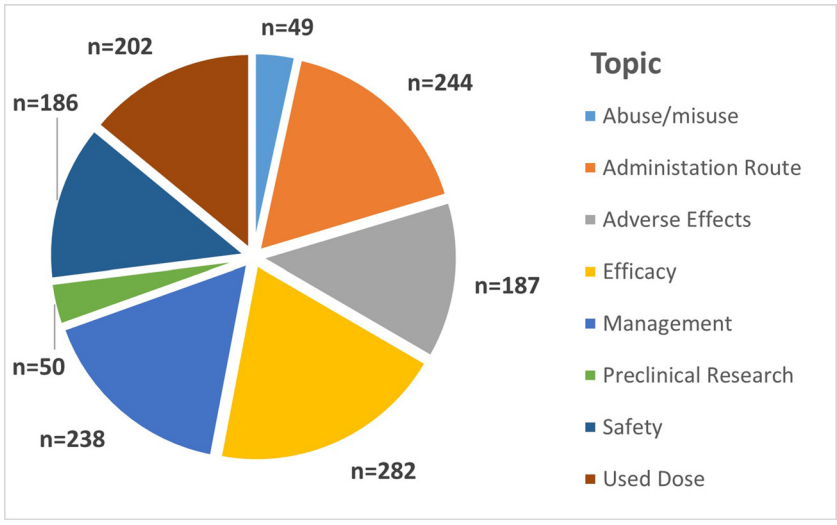

Fig. 4. Topics. One or more topics were recorded for each article.

appropriateness of using ROOs, regarding the type of pain (incident or spontaneous) and the clinical context for safer use.

Research should experiment with strategies useful for the description of the pathology and improve its treatment. For these purposes, telemedicine could offer interesting opportunities. In this way, a trial is ongoing to evaluate the features of cancer pain through remote monitoring solutions. It is aimed at collecting data and characterizing the BTcP

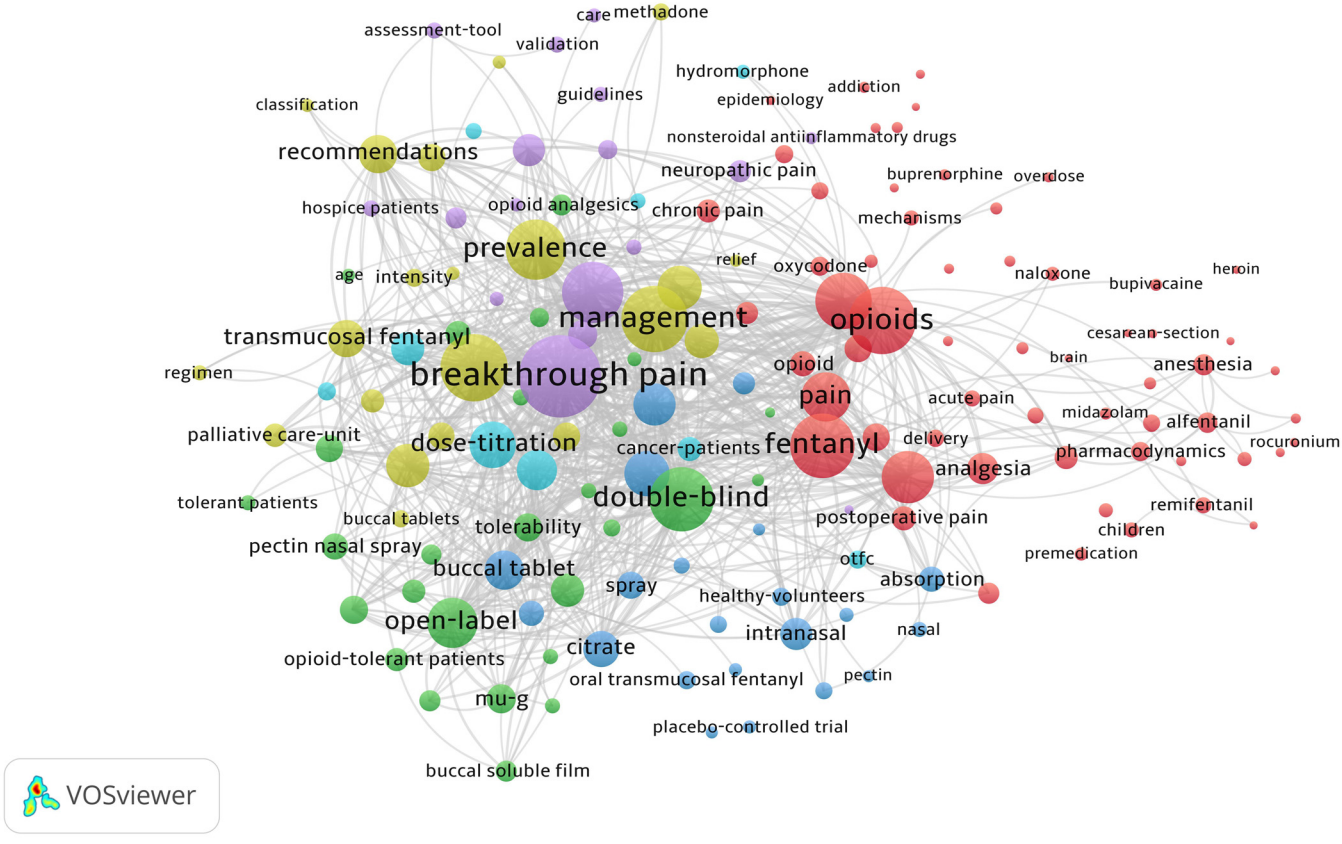

Fig. 5. Co-occurrence of keywords. The size of nodes indicates the frequency of occurrence. The curves between the nodes represent their co-occurrence in the same publication. The shorter the distance between two nodes, the larger the number of co-occurrence of the two keywords. The analysis provided 1,874 keywords; of those, 155 met the threshold (5 times) and 6 clusters were obtained (different colors).

Table 2
Top 10 Co-cited Articles

Author [Ref]	Title	Journal	Year	Topic	Citations
Farrar JT [15]	Defining the clinically important difference in pain outcome measures	Pain	2000	Pain assessment	725
Minto CF [16]	Pharmacokinetics and Pharmacodynamics of Remifentanil: II. Model Application	Anesthesiology	1997	Comparative study (PD)	454
Hernandez-Avila CA [17]	Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment.	Drug Alcohol Depend	2004	Substance abuse	343
Farrar JT [18]	Clinically important changes in acute pain outcome measures: a validation study	J Pain Symptom Management	2003	Pain measures	310
Davies AN [19]	The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland	Eur J Pain	2009	Guidelines on BTcP	288
Ripamonti CI [20]	Management of cancer pain: ESMO Clinical Practice Guidelines	Ann Oncol	2012	Guidelines on cancer pain	284
Mercadante S [21]	Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care	Cancer	2002	Consensus	238
Coluzzi PH [22]	Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR)	Pain	2001	RCT on ROOs	236
Scott JC [23]	Electroencephalographic quantitation of opioid effect: comparative pharmacodynamics of fentanyl and sufentanil	Anesthesiology	1991	Comparative study (PD)	233
Caraceni A [24]	Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey	Palliat Med	2004	Survey on BTcP	214

Abbreviations: PD, pharmacodynamics; ROOS, rapid-onset opioids; RCT, randomized controlled trial; BTcP, breakthrough cancer pain.

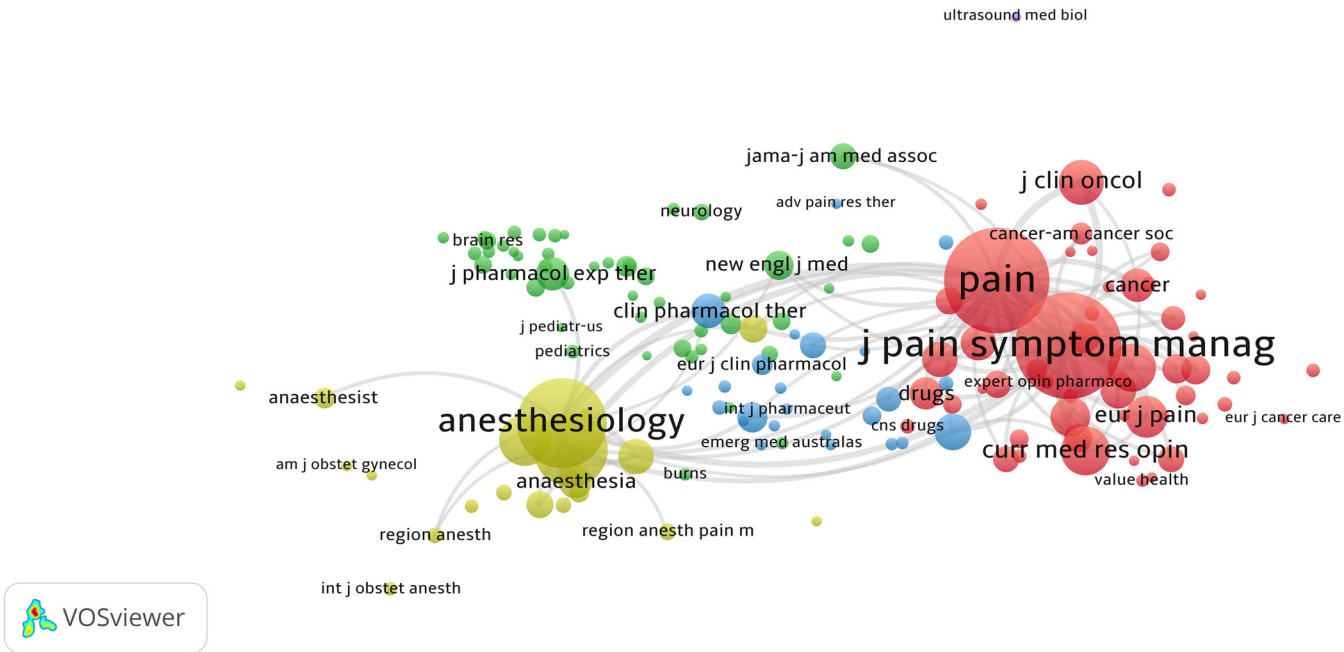

Fig. 6. Co-citation analysis for sources.

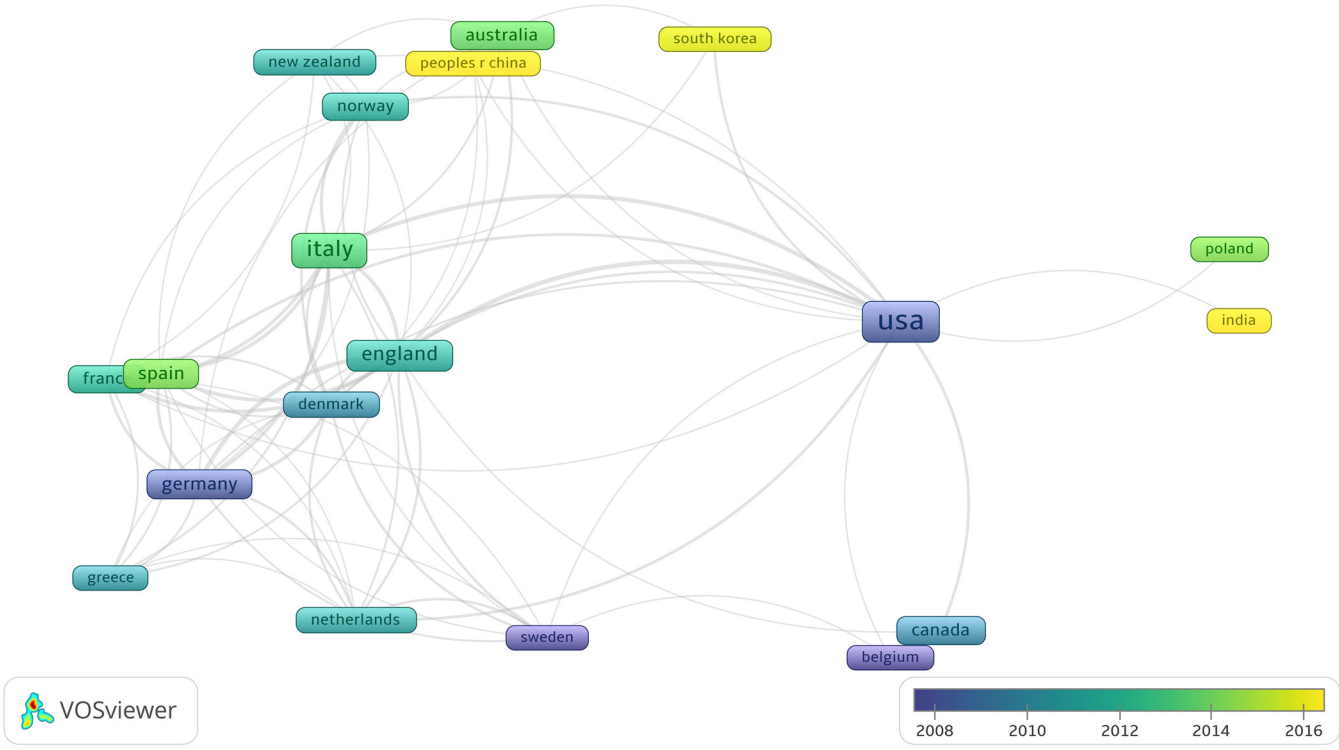

Fig. 7. Co-authorship analysis for countries. Nineteen countries reached the threshold of 5 documents. Clusters are organized for years' intervals.

phenomenon by using artificial intelligence resources (NCT04726228).

Most articles are published in high-ranked journals. Notably, about three-quarters of the articles are published by Q1 and Q2 journals. This indicates that BTcP treatment is a central topic of pain research. Some journals have paid close attention to the problem. For example, the Journal of Pain and Symptom Management, Anesthesiology, and Drugs published 39, 19, and 17 papers, respectively. The quality of the articles is expressed by a high number of citations. The most cited article (n = 725) was written by Farrar et al.,[18] in 2003.

A quarter of the articles concern clinical research. Of these, 13% are RCTs. Despite this number, a study that compared the Association for Palliative Medicine of Great Britain and Ireland guidelines (APM guidelines) to other national and international guidelines, concluded that the evidence to support actual guidelines is still of low grade.[1] Notably, we found 22 recommendations and guidelines. Many of these are different versions that update over the years. For example, the NCCN Clinical Practice Guidelines in Oncology for Adult Cancer Pain are revised every year.

The management of BTcP is addressed by about half of the articles. Arguments of paramount importance such as the patient-centered management of BTcP in patients with advanced cancer, as well as the impact of its treatment on quality of life, are stressed. On the other hand, the proper BTcP treatment requires further investigations. The lack of consensus probably stems from the gaps in the pathophysiology and clinical expressions of the phenomenon. For instance, different studies evaluated the clinical features of BTcP,[26] but the spontaneous subtype remains poorly studied. Moreover, although several formulations of ROOs have been released and there are numerous articles regarding their pharmacokinetic profile, there is no head-to-head comparison in clinical trials. This can add uncertainty to properly address the treatment. Furthermore, according to Mercadante et al.,[27] the challenge of ROOs dosing (proportional to the dose administered for background analgesia or to be titrated) calls for new large-size multicenter studies.

Some types of study have the objective of verifying the correct use of drugs, the management of complications, as well as the degree of knowledge about the matter, the iatrogenic misuse of ROOs, and other key topics. These data cannot come from clinical trials; however, surveys can offer answers to unsolved questions. For example, a recent survey demonstrated a high rate of inappropriate prescription behavior among physicians and the use of transmucosal fentanyl preparations beyond indication.[28] Although in our analysis we found 17 surveys, this type of research should be encouraged.

The semantic network investigation represents the core of each network analysis. It indicates the objectives of the research in a field. In our analysis, interesting

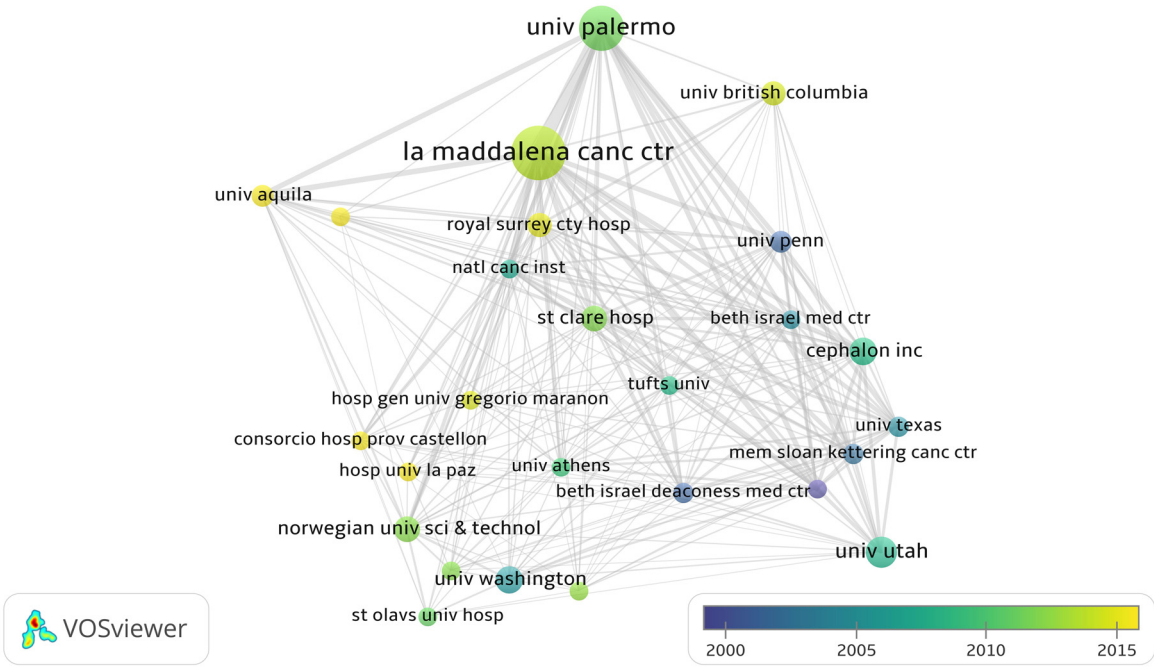

Fig. 8. The most productive organizations and collaboration links.

findings emerged. In particular, the interconnection between terms showed poor attention to very topical issues, such as addiction, overdose, and misuse. Notably, in their survey, Cahill et al. [29] found that about 30% of palliative medicine specialists affirmed they had had patients with suspected ROOs abuse. Previously, other reports focused on this phenomenon in a terminal cancer patient setting.[30] In the light of the recent opioid crisis,[31] addiction-related outcomes are as important as adequate pain relief, particularly with regards to the increasing population of cancer survivors.[32] There is no research focused on the relevant issue of addiction induced by (and not associated with) ROOs.

Presumably, more investigations are needed in this research area.

The research is disseminated in different countries. However, most of the co-authorship regards the United States, Italy, and England. The analysis of collaborations between research centers has highlighted an important gap. The most fruitful collaborations (at least 5 documents) involved a small number of centers (26/901). Since the studies with greater weight are produced by multicenter collaborations, additional networks should be built.

Limitations

A bibliometric analysis does not draw conclusions useful for the goals of evidence-based medicine. Nevertheless, clustering techniques applied to bibliometric datasets offer a quick overview that, in terms of graphic representation, is highly effective. Moreover, the number of items to be analyzed represents a limit in this strategy. In particular, a great number of documents may force a re-evaluation of the thresholds. The result is an underestimation of the represented results. Considering that our bibliometric research produced a relatively small number of elements, the analysis was carried out on all selected papers.

Another limitation is the use of a single software. We preferred VOSviewer because it focuses on visualizations at an aggregate level. On the other hand, tools like CitNetExplorer are more suitable for visualizations at the level of individual publications.[33]

The most important limitation of this analysis is structuring the underlying network. In particular, the linkage among publications is the result of citations or word relations. Consequently, keywords, the number of cited words (e.g., throughout the text), affiliations, and other elements have a great weight in the result representation. The reader must be aware of these limitations and bibliometric studies cannot replace systematic reviews or metanalysis.

Conclusions

This bibliometric network analysis on ROOs-based BTcP treatment can represent a useful instrument for planning future research. It highlighted the strength of representative scholars and core research teams. On the other hand, several gaps emerged. For example, research should focus on new strategies useful for the description of the disease. Moreover, additional

networks should be built, and high-value clinical studies are needed. Our co-author analysis shows that BTcP is still an issue for a few researchers and new networks are only recently emerging from countries previously not involved. It would be interesting to investigate whether ROOs are available in those countries and what is the standard treatment for BTcP. Finally, paramount topics such as opioid-induced abuse/misuse should be better addressed.

Author contributions

Dr Cascella conceptualized and designed the study, designed data collection instruments, collected data, completed initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Dr Monaco, Nocerino, Vittori, Carpenedo, Franceschini, Picerno, Migliaccio, Armignacco, and Chinè assisted with data collection instruments. M. Tracey and Forte reviewed and revised the manuscript. Dr Crispo, Coluccia, Tafuri, and Di Gennaro performed data analysis. Prof Cutugno performed the linguistic analysis. Prof Natoli and Cuomo coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Disclosures and Acknowledgments

The authors have no financial relationships relevant to this research to report. The authors thank Ms Maria Cristina Romano for her collaboration and assistance in reviewing the instruments and design of the study. The authors declare no conflicts of interest.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Davies AN, Elsner F, Filbet MJ, et al. Breakthrough cancer pain (BTcP) management: a review of international and national guidelines. BMJ Support Palliat Care 2018;8:241–249. https://doi.org/10.1136/bmjspcare-2017-001467.

2. Mercadante S, Lazzari M, Reale C, et al. Italian oncological pain survey (IOPS): a multicentre Italian study of breakthrough pain performed in different settings. Clin J Pain 2015;31:214–221. https://doi.org/10.1097/AJP.0000000000000161.

3. Camps Herrero C, Batista N, Díaz Fernández N, et al. Breakthrough cancer pain: review and calls to action to improve its management. Clin Transl Oncol 2020;22:1216–1226. https://doi.org/10.1007/s12094-019-02268-8.

4. Cuomo A, Cascella M, Forte CA, et al. Careful breakthrough cancer pain treatment through rapid-onset transmucosal fentanyl improves the uality of life in cancer patients: results from the BEST multicenter study. J Clin Med 2020;9:1003. https://doi.org/10.3390/jcm9041003.

5. Marchetti G, Vittori A, Tortora V, et al. Prevalence of pain in the departments of surgery and oncohematology of a paediatric hospital that has joined the project "Towards pain free hospital". Clin Ter 2016;167:156–160. https://doi.org/10.7417/CT.2016.1948.

6. Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO clinical practice guidelines. Ann Oncol. 2018;29(Suppl. 4):iv166–iv191. https://doi.org/10.1093/annonc/mdy152.

7. WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents. [(accessed on 26 December 2021)]; Available online: https://apps.who.int/iris/bitstream/handle/10665/279700/9789241550390-eng.pdf?ua=1.

8. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol 2012;13:e58–e68.

9. Cascella M, Crispo A, Esposito G, et al. Multidimensional statistical technique for interpreting the spontaneous breakthrough cancer pain phenomenon. A secondary analysis from the IOPS-MS study. Cancers (Basel) 2021;13:4018.. Published 2021 Aug 10. doi:10.3390/cancers13164018.

10. Yu Y, Li Y, Zhang Z, et al. A bibliometric analysis using VOSviewer of publications on COVID-19. Ann Transl Med 2020;8:816. https://doi.org/10.21037/atm-20-4235.

11. Xie L, Chen Z, Wang H, et al. Bibliometric and visualized analysis of scientific publications on atlantoaxial spine surgery based on web of science and VOSviewer. World Neurosurg 2020;137:435–442.e4. doi: 10.1016/j.wneu.2020.01.171.

12. Cascella Marco. Dataset_ROOS_BTCP [Data set]. Zenodo 2022. https://doi.org/10.5281/zenodo.5813333 Dataset.

13. Wu H, Yamaguchi A. Semantic web technologies for the big data in life sciences. Biosci Trends 2014;8:192–201. https://doi.org/10.5582/bst.2014.01048.

14. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics 2010;84:523–538.

15. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000;88:287–294.

16. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology 1997;86:24–33.

17. Hernandez-Avila CA, Rounsaville BJ, Kranzler HR. Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. Drug Alcohol Depend 2004;74:265–272.

18. Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. J Pain Symptom Manage 2003;25:406–411.

19. Davies AN, Dickman A, Reid C, et al. The management of cancer-related breakthrough pain: recommendations of a task group of the science committee of the association for palliative medicine of great britain and Ireland. Eur J Pain 2009;13:331–338.

20. Ripamonti CI, Santini D, Maranzano E, et al. Management of cancer pain: ESMO clinical practice guidelines. Ann Oncol 2012;23(Suppl 7):vii139-54.

21. Mercadante S, Radbruch L, Caraceni A, et al. Steering Committee of the European Association for Palliative Care (EAPC) Research Network. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. Cancer 2002;94:832–839.

22. Coluzzi PH, Schwartzberg L, Conroy JD, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). Pain 2001;91:123–130.

23. Scott JC, Cooke JE, Stanski DR. Electroencephalographic quantitation of opioid effect: comparative pharmacodynamics of fentanyl and sufentanil. Anesthesiology 1991;74:34–42.

24. Caraceni A, Martini C, Zecca E, et al. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. Palliat Med 2004;18:177–183.

25. Lei F, Ye J, Wang J, Xia Z. A bibliometric analysis of publications on oxycodone from 1998 to 2017. Biomed Res Int 2019:9096201. 2019.

26. Caraceni A, Shkodra M. Cancer pain assessment and classification. Cancers (Basel) 2019;11:510. https://doi.org/10.3390/cancers11040510.

27. Mercadante S, Portenoy RK. Understanding the chameleonic breakthrough cancer pain. Drugs 2021;81:411–418. https://doi.org/10.1007/s40265-021-01466-5.

28. Wirz S, Schenk M, Hofbauer H, et al. Nicht-indikationsgemäßer Einsatz schnell freisetzender Fentanylzubereitungen: Stichprobenartige Fragebogenerhebung bei Kongressteilnehmern und Schmerzmedizinern [Use of rapid-onset fentanyl preparations beyond indication: a random questionnaire survey among congress participants and pain physicians]. Schmerz 2021;35:114–123. https://doi.org/10.1007/s00482-020-00503-8. German.

29. Cahill K, Shehab RM, Hassan A, et al. Addiction to transmucosal fentanyl: is it a cause for concern in cancer pain management? Palliat Med 2015;29:861–862. https://doi.org/10.1177/0269216315593452.

30. Nunez-Olarte J, Alvarez-Jimenez P. Emerging opioid abuse in terminal cancer patients taking oral transmucosal fentanyl citrate for breakthrough pain. J Pain Symptom Manage 2011;42:e6–e8.

31. Ciccarone D. The triple wave epidemic: supply and demand drivers of the US opioid overdose crisis. Int J Drug Policy 2019;71:183–188. https://doi.org/10.1016/j.drugpo.2019.01.010.

32. Carmona-Bayonas A, Jiménez-Fonseca P, Castañón E, et al. Chronic opioid therapy in long-term cancer survivors. Clin Transl Oncol 2017;19:236–250. https://doi.org/10.1007/s12094-016-1529-6.

33. van Eck NJ, Waltman L. Citation-based clustering of publications using CitNetExplorer and VOSviewer. Scientometrics 2017;111:1053–1070. https://doi.org/10.1007/s11192-017-2300-7.