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Global Trends in Oliceridine (TRV130) Research from 2013 to 2024: A Bibliometrics and Knowledge Graph Analysis

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Purpose: The adverse effects and drug abuse issues associated with opioid drugs have made finding a safe and effective alternative a focus of research. Oliceridine has attracted attention for its lower adverse reactions, such as respiratory depression and gastrointestinal issues, compared to traditional opioids, and is considered a promising candidate for addressing the current limitations in opioid therapy. This article explored the knowledge structure of oliceridine through bibliometric analysis, highlighting its clinical applications in managing acute pain and its mechanisms that may reduce addiction risk. Our bibliometric analysis highlighted hotspots and trends in oliceridine research, guiding future studies on its safety and efficacy in pain management.

Methods: This study utilized the Web of Science Core Collection database to search for articles related to oliceridine from 2013 to 2024. Systematic analysis was conducted on publication, country, institution, author, journal, references, and keywords. The software Citespace, Vosviewer, and Bibliometrix were employed to visualize bibliometric analysis.

Results: From 2013 to 2024, 159 articles on oliceridine were published in 98 journals by 158 institutions from 28 countries. The United States has rapidly developed in this field, providing significant momentum. Keyword clustering analysis revealed that research on oliceridine primarily focused on exploring its molecular and pharmacological mechanisms and conducting clinical studies to evaluate its efficacy and safety in pain management. Analyses of the strongest citation bursts with references and keywords indicated that protein-biased ligands and oliceridine were hotspots. The emergence of divergent views regarding oliceridine's biased agonism will lead to future hotspots focusing on the underlying mechanisms of biased signaling by G protein-coupled receptors and drug design.

Conclusion: Bibliometric analysis provides insights into the current hotspots and emerging areas of oliceridine, which can guide future research. The widespread attention and clinical application of oliceridine lay a solid foundation for further drug development and clinical trials.

Keywords: opioid receptors, biased agonism, oliceridine, bibliometrics

Introduction

Pain represents a global public health issue, with opioid medications considered the primary choice for effective pain relief. However, adverse reactions associated with opioid drugs can limit their optimal analgesic dosage. These adverse reactions decrease patient compliance and reduce their quality of life. Moreover, the abuse of opioid drugs is a significant social problem. Therefore, the objective of opioid analgesic drug development has consistently been to create μ-opioid receptor agonists with high affinity and specificity.

The μ-opioid receptor belongs to the G protein-coupled receptor family, which is a cell surface receptor that binds to extracellular substances and transmits intracellular signals through G proteins.[1] The interaction of opioid drugs with the μ-opioid receptor triggers signaling through the G protein and the β-arrestin pathways. Stimulation of the G protein pathway produces analgesic effects. In contrast, activation of the β-arrestin pathway is associated with opioid-related

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adverse events.[2] The focus on biased agonism is crucial because it allows for the selective activation of the G protein pathway while minimizing β-arrestin activation. This differentiation has the potential to separate therapeutic benefits from harmful side effects, leading to safer pain management options and a reduced risk of opioid-related complications. In attempts to reduce side effects, an increasingly exciting area is the design of opioid drugs that activate one pathway rather than another.[3–8] Bohn and colleagues found that morphine maintained its analgesic efficacy without tolerance in β-arrestin 2 gene knockout animals, which subsequently led to the development of TRV130.[9,10] TRV130 is a novel G protein-biased μ-opioid receptor agonist. It activates G protein signaling while causing minimal recruitment of β-arrestin proteins.[3] Trevena led the development of TRV130, later renamed as oliceridine. Intravenous injection of oliceridine has shown superior analgesic effects compared to placebo in patients with moderate to severe postoperative pain. Compared to morphine, it exhibits good safety and tolerability in terms of respiratory and gastrointestinal adverse reactions. The US Food and Drug Administration has approved the Olinvyk (Oliceridine) injection solution for treating moderate to severe acute pain in adults.

Bibliometric analysis is a quantitative method that examines the distribution characteristics, knowledge structure, and development trends of literature based on the external features of scientific literature, such as authors, keywords, and citations. The research findings will offer guiding suggestions for researchers' subsequent decision-making. In recent years, with the deepening research on oliceridine, there has been a need for bibliometric studies on oliceridine. We utilized Vosviewer, Citespace, and Bibliometrix to analyze oliceridine-related literature comprehensively.

Methods

Data Collection and Retrieval Strategy

This study selected literature from the Web of Science Core Collection (WOSCC) database, and the search formula is as follows: (((((TS=(oliceridine)) OR TS=(Olinvyk)) OR TS=(TRV-130)) OR TS=(TRV130))). There were no language restrictions, and the document types were limited to articles and reviews. The search time range was from January 1, 2013, to February 29, 2024. To avoid errors caused by database updates, the search was completed within one day on March 1, 2024. Assign two researchers to screen the literature and remove irrelevant articles independently. If there is ambiguity regarding the inclusion of literature, a third researcher will be introduced to discuss whether the article should be included in the study. After screening, a total of 159 articles were included for bibliometric analysis. Retrieved literature records were saved as plain text files, formatted as "full record and cited references". The following information was extracted: year of publication, journal, impact factor, title, author, country, institution, reference, keywords, number of citations, the number of citations average, and H-index.

This study utilized publicly available data and was exempt from ethics approval according to Notice on the Issuance of Ethical Review Measures for Life Science and Medical Research involving Humans (National Health Science Education Development [2023] No. 4). The data analyzed did not involve direct interaction with human participants, and the use of anonymized data falls within the provisions outlined by Declaration of Helsinki.

Statistical Methods

This study utilizes Citespace (version 6.2.4) visualization software. The parameters were set from 2013 to 2024, with analysis conducted in one-year time slices and nodes selected for country, institution, author, reference, and keyword. Top N=50 was chosen as the selection criteria, with other attribute values set to default parameters. This threshold captures a significant portion of the data while ensuring representation of the most influential authors in each time slice, striking a balance between comprehensiveness and clarity in our results. The Pathfinder pruning method was selected to optimize the network structure. In this study, cooperation network analyses of country, institution, author, references with the strongest citation bursts, and keywords with the strongest citation bursts were plotted. Nodes with purple outer rings indicate higher centrality. This study utilized Bibliometrix software, run on R 4.1.3, to extract the most locally cited documents and most locally cited references.

In this study, Vosviewer software was used for keyword clustering visualization analysis. The software operates on bibliographic coupling and co-citation principles, constructing a graph based on node size, density, and distance

differences to explore research directions and hotspots. The analysis employed co-occurrence as the type, considered all keywords as the unit of analysis and utilized full counting as the counting method. Synonyms were merged as well.

Citespace is primarily used for analyzing collaboration networks among countries, institutions, and authors, as well as for generating burst maps for keywords and references. VOSviewer specializes in clustering keywords and creating timeline visualizations to illustrate the evolution of research themes over time. Bibliometrix is designed to identify influential articles within the field, providing a robust framework for extracting key insights from bibliometric data. While bibliometric tools are useful for analyzing bibliometric trends, they each possess limitations that should be acknowledged. Database reliance can narrow the scope, and complex relationships may be simplified in visualizations.

Results

Trends in Literature Publishing Output

Figure 1 displays the annual publication and citation trends of oliceridine. A total of 159 articles on oliceridine were published from 2013 to 2024. There was a significant increase from 2013 to 2021, with an annual growth rate of 3.75%. The significant increase in publications between 2013 and 2021 can be attributed to key clinical milestones, particularly the FDA approval of oliceridine in 2020, which spurred research interest and subsequent publications in the field. The total citation count for the articles is 4856, which decreases to 3635 after self-citations are excluded. In 2022, the citation count reached 1067.

Collaboration Network Analysis

The 159 articles mainly come from 28 countries (Table 1). The United States leads in publication count, contributing 62.89% (100 out of 159 articles) of the total publications. The total citation count is 3742, with an average citation frequency of 36.69 and an H-index of 29, indicating significant influence in this field. The countries ranked 2nd to 11th in publication volume are China, England, Italy, Australia, Germany, Canada, Poland, France, Japan, and South Korea. Figure 2A depicts the country collaboration network with a density of 0.15, indicating relatively sparse international collaboration. This may result from interconnected factors such as political tensions, economic disparities, cultural differences, and technological gaps. Geographical distance, varying national policies, and language barriers further hinder effective cooperation. Centrality values show that the USA is 0.9, Germany is 0.44, and Canada is 0.29, indicating these countries' significant intermediary roles and strong control capabilities over the network. The USA collaborates with England, Germany, and Italy, while Germany collaborates closely with England, New Zealand, and Australia.

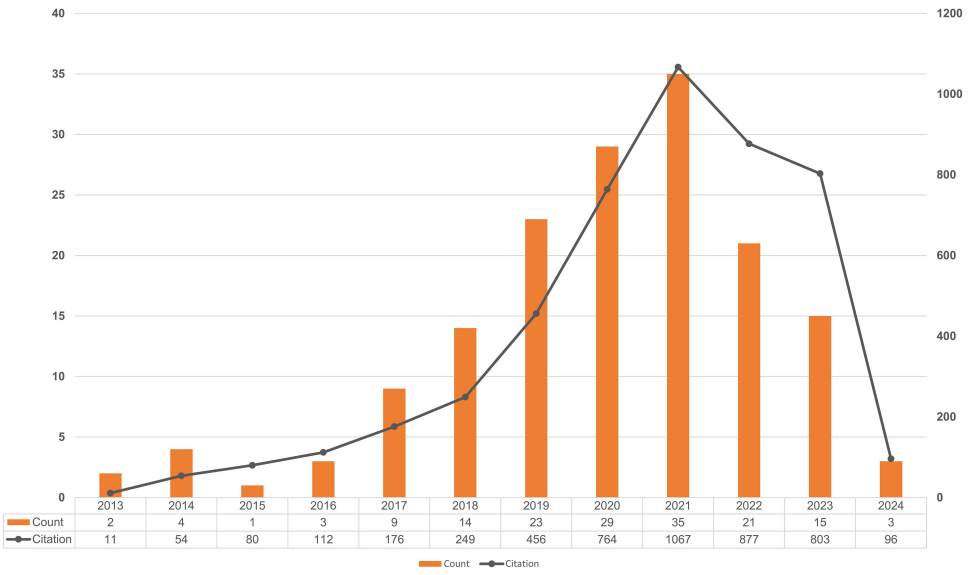

Figure 1 Trends in annual publications and citations related to oliceridine.

Table 1 Top 11 Countries According to the Total Number of Publications

Rank	Countries	Count	Centrality	Begin Year
1	USA	100	0.9	2013
2	PEOPLES R CHINA	21	0.16	2017
3	ENGLAND	15	0.18	2018
4	ITALY	9	0.18	2019
5	AUSTRALIA	8	0.09	2018
6	GERMANY	6	0.44	2018
7	CANADA	5	0.29	2014
8	POLAND	5	0.16	2017
9	FRANCE	5	0.15	2014
10	JAPAN	5	0	2017
11	SOUTH KOREA	5	0	2018

A total of 158 institutions worldwide are involved in oliceridine research. Table 2 demonstrates that the top 10 institutions, comprising 66 publications, are exclusively from the United States, representing 41.51% of all publications (66 out of 159). DUKE UNIVERSITY ranks first in publication volume with 9 articles, accounting for 5.66% (9/159), and an H-index of 7, indicating that there are 7 papers which have each been cited at least 7 times. The H-index measures both the productivity and citation impact of researchers or institutions. It is defined as the number of publications that have received at least the same number of citations as the count of those publications, reflecting both the quantity and quality of their work. By examining the H-index across different authors and institutions, we can identify key players and assess their contributions to the development of oliceridine.

The institution collaboration network (Figure 2B) has a density of 0.02, indicating a relatively loose level of collaboration between institutions, characterized by small-group cooperative relationships.

Table 3 presents the top 10 highly productive authors from the USA. Fossler, Michael J. is the most productive author, with 13 published articles cited 266 times, an average citation frequency of 20.46, and an H-index of 7. The USA's concentrated research output is driven by significant funding opportunities, institutional priorities that emphasize research initiatives, and supportive governmental policies that foster collaboration and innovation. Figure 2C depicts the author's collaboration network with a density of 0.02. The figure shows many sub-networks in the collaboration network, indicating regional small-group clustering in the research. Fossler, Michael J. and Soergel, David G. have significantly contributed to oliceridine research.

Journal Publication Analysis

Between 2013 and 2024, 98 journals published articles related to oliceridine (Table 4). The top 13 journals accounted for 51 publications, cumulatively representing 32.08%. Among them, articles were published in

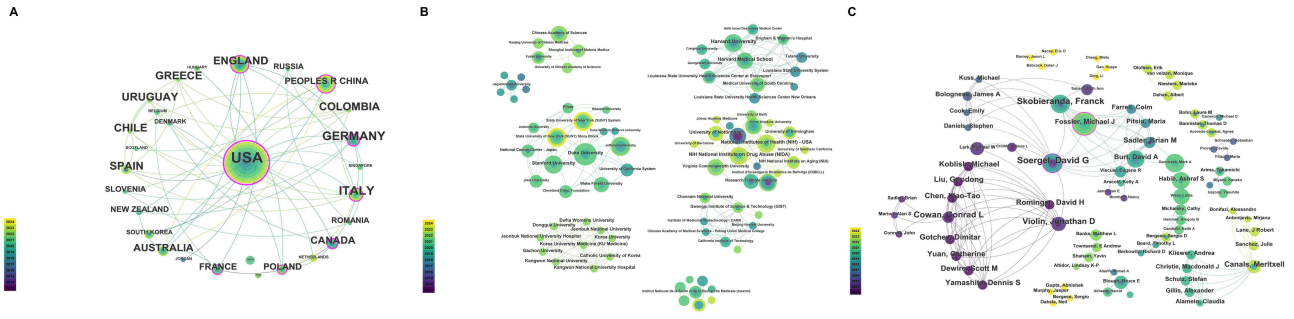

Figure 2 Cooperation network among (**A**) countries, (**B**) institutions, and (**C**) authors.

Table 2 Top 10 Institutions According to the Total Number of Publications

Rank	Institutions	Country	Count	Total citation	Average citation	H-index
1	DUKE UNIVERSITY	USA	9	174	19.33	7
2	STATE UNIVERSITY OF NEW YORK (SUNY) STONY BROOK	USA	7	708	78.67	6
3	STATE UNIVERSITY OF NEW YORK (SUNY) SYSTEM	USA	7	708	78.67	6
4	JEFFERSON UNIVERSITY	USA	7	371	53	5
5	NATIONAL INSTITUTES OF HEALTH (NIH)	USA	6	80	11.43	4
6	NIH NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)	USA	6	80	11.43	4
7	RESEARCH TRIANGLE INSTITUTE	USA	6	236	33.71	4
8	VIRGINIA COMMONWEALTH UNIVERSITY	USA	6	198	28.29	5
9	HARVARD UNIVERSITY	USA	6	71	11.83	5
10	STANFORD UNIVERSITY	USA	6	107	17.83	5

Table 3 Top 10 Most Productive Authors According to the Total Number of Publications

Rank	Authors	Country	Count	Total citation	Average citation	H-index
1	Fossler, Michael J.	USA	13	266	20.46	7
2	Skobieranda, Franck	USA	11	736	66.91	8
3	Demitrack, Mark A.	USA	11	211	19.18	6
4	Soergel, David G.	USA	11	1080	98.18	9
5	Wase, Linda	USA	9	138	15.33	6
6	Habib, Ashraf S.	USA	8	144	18	6
7	Blough, Bruce E.	USA	7	236	33.71	4
8	Burt, David A.	USA	7	375	53.57	7
9	Violin, Jonathan D.	USA	6	1200	200	6
10	Viscusi, Eugene R.	USA	6	370	61.67	5

BRITISH JOURNAL OF PHARMACOLOGY (n=6, 3.77%), FRONTIERS IN PHARMACOLOGY (n=6, 3.77%), and JOURNAL OF PAIN RESEARCH (n=5, 3.14%). Eight of these 13 journals are listed in the JCR1 zone. The JOURNAL OF PAIN RESEARCH achieved the highest total citation frequency of 893.

High-Cited Articles and High-Cited References

The citation index reflects the number and frequency of citations of a specific document within a certain time frame. The article "A G protein-biased ligand at the μ-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine", published in 2013, has the highest citation frequency (Figure 3A). This article first reported the discovery of TRV130. Other highly cited articles are mostly clinical trials of TRV130, which demonstrate that oliceridine is a safe and effective intravenous analgesic for treating moderate to severe acute pain with less respiratory depression and gastrointestinal adverse effects.

The top-ranked article in Local High-cited references (Figure 3B) is still the first discovery of TRV130 published by DEWIRE SM in 2013. Articles ranked 2–4 mainly discuss the mechanisms underlying the adverse effects of opioid analgesics. APOLLO-1 and APOLLO-2, published in 2019, are two randomized, placebo, and active-controlled Phase III studies evaluating the efficacy and safety of oliceridine in treating moderate to severe acute pain following abdominal surgery and postoperative recovery from bunionectomy.

Figure 3C illustrates the burst map of the top 25 references. The timeline indicates that before the discovery of TRV130, research was predominantly focused on "biased agonism." This suggests that before this discovery, the scientific community had already shown interest in biased agonists. The discovery of TRV130 marked a significant turning point. Following validation through in vitro and in vivo experiments, TRV130 was identified as an effective

Table 4 Top 13 Journals of the Most Publications Related to Oliceridine

Rank	Journal	Count	Percentage (%)	Cumulative percentage (%)	IF	Quartile in Category	Total citation	Average citation	H-index
1	BRITISH JOURNAL OF PHARMACOLOGY	6	3.77	3.77	7.3	Q1	137	22.83	5
2	FRONTIERS IN PHARMACOLOGY	6	3.77	7.55	5.6	Q1	93	15.50	2
3	JOURNAL OF PAIN RESEARCH	5	3.14	10.69	2.7	Q3	869	173.80	5
4	INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	4	2.52	13.21	5.6	Q1	14	3.50	2
5	PAIN AND THERAPY	4	2.52	15.72	4.0	Q2	37	9.25	3
6	PAIN	4	2.52	18.24	7.4	Q1	373	93.25	3
7	ANESTHESIOLOGY	4	2.52	20.75	8.8	Q1	52	13	3
8	MOLECULAR PHARMACOLOGY	3	1.89	22.64	3.6	Q2	139	46.33	3
9	EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY	3	1.89	24.53	6.7	Q1	42	14	3
10	JOURNAL OF CLINICAL PHARMACOLOGY	3	1.89	26.42	2.9	Q3	123	41	3
11	JOURNAL OF MEDICINAL CHEMISTRY	3	1.89	28.30	7.3	Q1	196	65.33	2
12	CLINICAL PHARMACOLOGY IN DRUG DEVELOPMENT	3	1.89	30.19	2.0	Q4	33	11	2
13	NEUROPHARMACOLOGY	3	1.89	32.08	4.7	Q1	154	51.33	3

Notes: Journal Citation Reports rankings sort all journals within a given discipline in descending order based on the previous year's impact factor. These journals are then divided into four quartiles: Q1, Q2, Q3, and Q4. Q1 represents the top 25% of journals with the highest impact factors, while Q4 includes those in the bottom 25%.
Abbreviations: IF, Impact Factor (2023).

biased agonist of the μ-opioid receptor with a lower risk of adverse reactions. Subsequent clinical trials further confirmed its effectiveness and safety in acute pain management. In 2020, the FDA approved the market launch of the analgesic Olinvyk.

Keyword Analysis

Keyword-based analysis can reflect the evolving trends and research hotspots of a specific research field over a certain period. This study conducted a co-word clustering analysis on 60 high-frequency keywords with frequencies ≥6 (Figure 4A). The blue cluster focuses on the mechanism research of biased agonism, mainly including terms such as ligand, analgesic, biased agonism, and 28 other keywords. The red cluster revolves around research related to the drug TRV130, including terms such as trv130, biased ligand, pain, and other 10 keywords. The green cluster mainly centers on research related to TRV130 being renamed as oliceridine, including terms such as oliceridine, mu-opioid receptor, management, and other 22 keywords. The blue cluster, centered on "biased agonism", points toward an emerging interest in precision medicine within opioid pharmacology. Biased agonism, which selectively targets certain signaling pathways over others, represents a shift away from traditional opioid mechanisms. Recent research, as well as ongoing oliceridine clinical trials, suggests that this approach could lead to more tailored treatments, reducing risks like addiction and respiratory depression.

Biased agonism has gained significant attention as it moves from basic research to clinical applications. Oliceridine is one of the first biased agonists approved for clinical use. Recent clinical trials have explored its potential in pain management, showing promise in minimizing adverse effects. The presence of terms like "protein-biased ligand" and "oliceridine" in the keyword clusters highlights a shift in focus toward developing more effective and safer treatments. This trend reflects the growing interest in translating biased agonism into real-world clinical solutions.

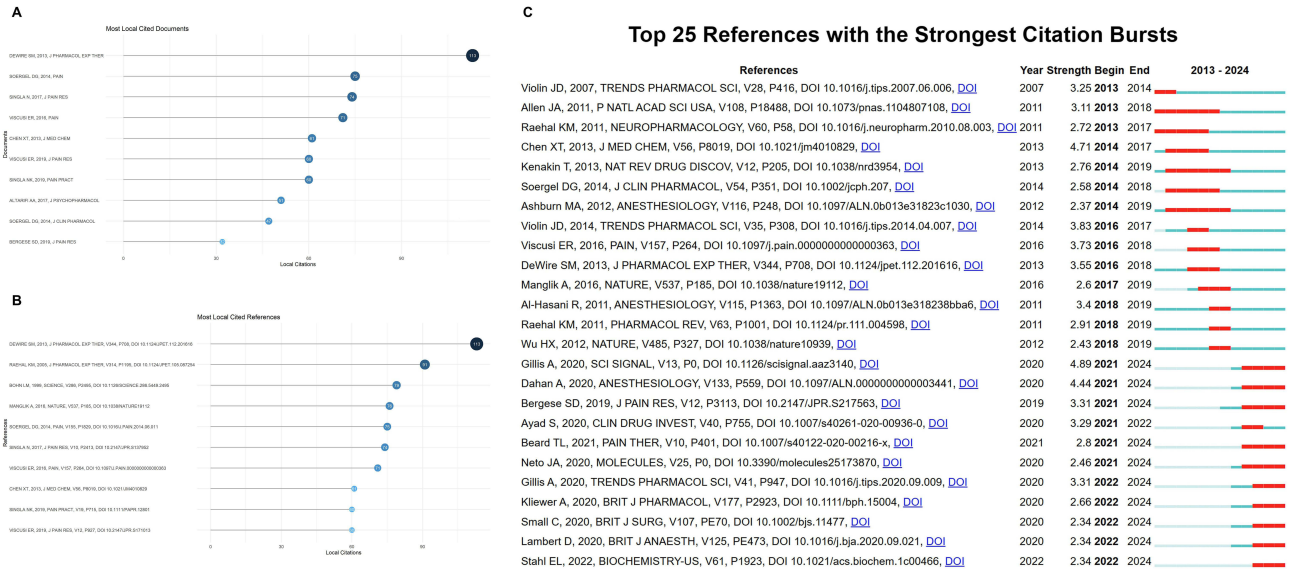

Figure 3 (**A**) Most local cited documents, (**B**) Most local cited references, and (**C**) Top 25 References with the Strongest Citation Bursts.

Figure 4B illustrates the timeline of keyword co-occurrence to identify emerging research themes. In this graph, darker node colors indicate earlier research, while lighter colors represent more recent topics. The yellow nodes specifically highlight emerging themes after 2021, including oliceridine, protein-biased ligands, moderate pain relief, and antinociception. These topics are considered emerging because they reflect recent advancements in pain management, particularly following the FDA approval of oliceridine in 2020, and the growing interest in developing selective protein-biased ligands to improve therapeutic outcomes. Additionally, there is an increased focus on alternative strategies for moderate pain relief amid the ongoing opioid crisis. This finding aligns with the analysis results of the top 25 keywords with the strongest citation bursts (Figure 5), further confirming the importance and prominence of these keywords in this field.

Discussion

General Information

This study visualized the global research status of oliceridine from 2013 to 2024 through bibliometric analysis, revealing the knowledge structure, research directions, and hotspots in this field. As of February 29, 2024, the WOSCC database

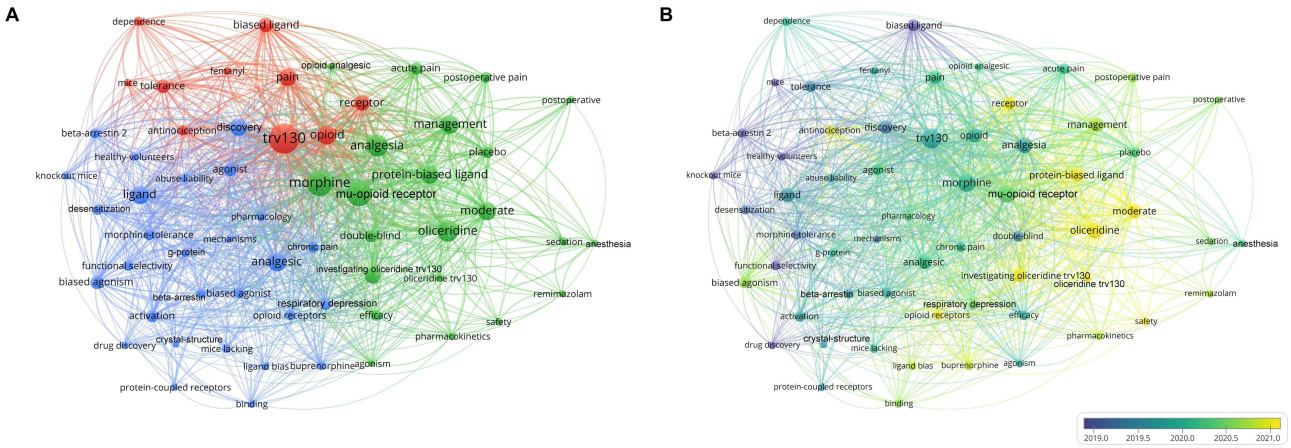

Figure 4 Keyword co-occurrence analysis and time graph. (**A**) Keyword co-occurrence analysis and, (**B**) Keywords analysis according to the average publication year.

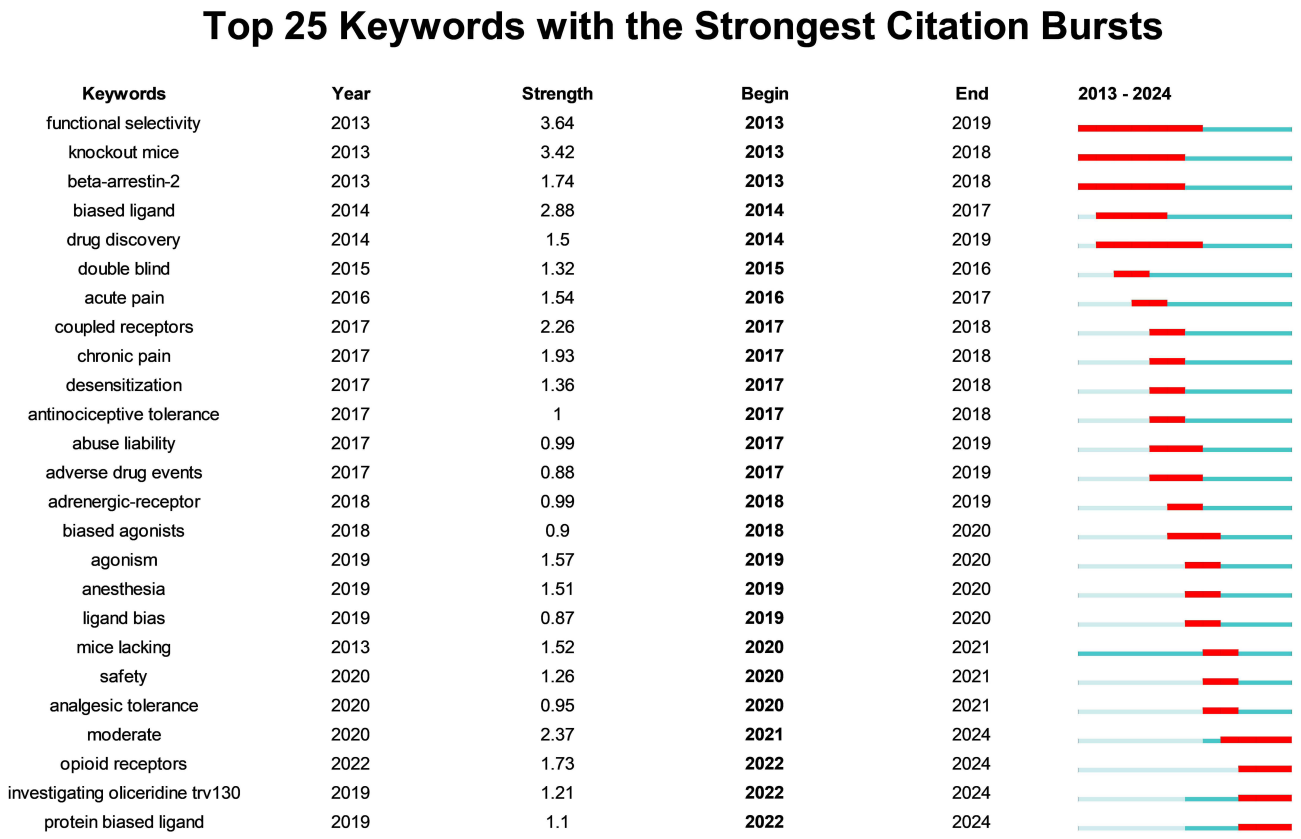

Figure 5 Top 25 Keywords with the Strongest Citation Bursts.

included 28 countries, 158 institutions, and 98 journals that published 159 articles on oliceridine. The research used quantitative analysis of publication volume to explore the changes in oliceridine research. Oliceridine research began in 2013 and has shown an overall upward trend. The United States emerges as the dominant player, leading in article quantity and the presence of the top ten most productive institutions and authors. The statistical results show that this field is forming a group of stable and influential researchers and institutions. Researchers can benefit from reading these articles to quickly grasp the research foundation and can also choose to engage in communication and collaboration with these institutions or authors.

The Research Trends, Hotspots

Bibliometrics can help researchers understand the development trends and evolution patterns of disciplines. Analyzing literature output, hotspots, and keywords makes it possible to predict the direction of discipline development. Keywords are the core content of research topics in bibliometrics. Keyword clustering can describe the knowledge structure and reveal the forefront of research disciplines. The cluster analysis in this study shows three main clusters, clearly depicting the development process of biased agonism of the μ-opioid receptor. This process highlights the long journey of scientific research from the laboratory to clinical applications. Through continuous experimental validation and clinical trials, TRV130, a biased agonist, has ultimately achieved the translation from scientific discovery to clinical application. Despite advances in acute postoperative pain management, high prevalence persists, prompting renewed interest in multimodal analgesia, with Oliceridine, a novel mu-opioid receptor agonist, selectively activating G-protein signaling to enhance analgesic effects while minimizing opioid-related adverse events.[11]

In vitro studies have shown that oliceridine affects G protein activation, reduces β-arrestin recruitment, and decreases μ-opioid receptor internalization. Compared with morphine, oliceridine induces only 14% of β-arrestin signaling activity

in vitro.[12] In rodent models, oliceridine exhibits potent analgesic effects, with less nausea and vomiting than morphine.[13] Unlike morphine, oliceridine does not produce known active metabolites.[14]

Phase I studies reported a range of oliceridine use from 0.15 to 7 mg.[15] Another phase I study indicated that compared to 10 mg of morphine, a dose of 3mg or 4.5mg of oliceridine can improve analgesic effects and act more quickly. Additionally, oliceridine depressed respiratory function less than morphine, with nausea and vomiting observed only at a supratherapeutic dose of 7mg.[16]

A Phase II study found that oliceridine provided more significant pain relief than morphine, with meaningful pain relief occurring within 5 minutes.[17] In another randomized phase II study, Singla demonstrated that oliceridine for acute pain following abdominal surgery had good safety and tolerability, with a lower incidence of gastrointestinal dysfunction and respiratory depression compared to the morphine group.[14] The incidence of nausea and vomiting with the oliceridine increased dose-dependently.

The phase III Apollo trial described the good analgesic effect of oliceridine.[18,19] The patient-controlled analgesia regimen utilizing 0.35 mg of oliceridine exhibited efficacy comparable to morphine but with fewer adverse effects, thus achieving an optimal balance between analgesic efficacy and side effects. In a retrospective study of the two Apollo trials, oliceridine exhibited better gastrointestinal tolerability compared to morphine.[20] In an open-label phase III trial, Athena, oliceridine was found to have potent analgesic effects and is generally safe and well-tolerated in heterogeneous populations.[21] It is worth noting that patients participating in Athena are often older and have at least one comorbidity.

The research on oliceridine's abuse potential remains inconclusive. While oliceridine may be safer than traditional opioids regarding side effect profiles and the risk of respiratory depression, current evidence indicates that it still possesses opioid-like abuse potential. Notably, a study found that knockout of β-arrestin-2 did not diminish the rewarding effects of morphine; rather, it enhanced morphine-induced conditioned place preference in β-arrestin-2 knockout mice. This suggested that the rewarding effects of morphine were not mediated by β-arrestin-2 signaling, implicating G protein signaling as a likely mediator of opioid reward in mice.[22] Additionally, TRV130 produced conditioned place preference in mice, although at a higher dose than that required for analgesia.[13] Some studies have focused on TRV130, which generally indicated that it retained an abuse potential comparable to that of commonly abused opioid analgesics.[23] Furthermore, the abuse potential of oliceridine is equivalent to that of non-biased μ-opioid receptor agonists like morphine and hydrocodone.[16,24] The rewarding effects of oliceridine appear to be dose-dependent, but at analgesic doses, it does not induce reward-related behaviors.[7] Interestingly, another study suggested that compared to buprenorphine, oliceridine reduced the seeking and use of hydrocodone in a gender-dependent manner during abstinence.[25]

Up to now, no apparent tolerance has been found after repeated treatment with oliceridine, a characteristic that distinguishes the drug among opioid analgesics acting through the μ receptor. Studies indicated that carboxyl-terminal phosphorylation regulated μ-opioid receptor desensitization and its interaction with β-arrestin 2.[26] β-arrestin 2 is a scaffold protein that binds to phosphorylated receptors, and the binding of phosphorylated receptors to β-arrestin 2 allows receptor internalization, resulting in fewer receptors available for further activation by agonists. These mechanisms are thought to underlie the reduction in agonist signaling following chronic agonist exposure.[27] Mori reported that oliceridine treatment did not induce rapid development of neuropathic tolerance in mice.[28] Like other recognized non-biased agonists, oliceridine induces opioid-induced hyperalgesia.[29]

The Frontiers

The analysis of the strongest citation bursts of references and keywords and keyword clustering analysis can reflect the evolution of themes and hotspots over a certain period. Some research findings challenge the previously held belief that β-arrestin 2 signaling plays a critical role in opioid-induced respiratory depression, raising concerns about the development of G-protein-biased μ-opioid receptor agonists as a safer alternative for opioid analgesics. Studies have shown that morphine and fentanyl still induce respiratory depression and constipation in β-arrestin 2 knockout mice, suggesting that the absence of β-arrestin 2 may not completely prevent these adverse effects.[30] Moreover, recent attempts to replicate the original findings using β-arrestin 2 knockout models have been unsuccessful, calling into question the reliability of the initial results.[31]

Further complicating the picture, the study on oliceridine indicates that its improved therapeutic window is primarily due to its lower intrinsic efficacy rather than its G-protein-biased signaling properties. This finding challenges the fundamental premise of developing G-protein-biased agonists as a means of reducing opioid-related side effects.[32]

Nevertheless, other studies support the notion that G-protein bias can enhance opioid analgesia while reducing adverse effects, showing consistency with earlier research.[33,34] These conflicting results suggest that the relationship between G-protein-biased signaling and opioid efficacy or safety is more complex than initially thought. As controversies and doubts about biased agonism continue to emerge, the focus of research is gradually shifting toward a deeper understanding of the intrinsic mechanisms driving G-protein-coupled receptor signaling. This shift in perspective will likely propel further in-depth studies, offering a more comprehensive theoretical foundation and technical advancements for future drug development and clinical applications.

In the future, it is necessary to explore the safety and effectiveness of oliceridine in obstetric and pediatric populations, given their heightened vulnerability to adverse reactions from opioid medications. Additionally, there is a pressing need to elucidate the role of oliceridine in Enhanced Recovery After Surgery (ERAS) protocols, particularly considering the emphasis on multimodal analgesia to mitigate opioid usage and its associated adverse effects. Despite the incorporation of oliceridine into multimodal analgesia regimens in the Athena trial, further data is warranted to ascertain its safety and efficacy when used concomitantly with other analgesics.

Strengths and Limitations

With the continuous development of computer science, academic research has gradually shifted from traditional laboratory research to digitalized and networked research, which has attracted more attention to bibliometrics. Bibliometric analysis identifies research gaps by mapping existing literature, helping researchers focus on under-explored topics. It reveals publication trends that indicate shifts in research focus, enabling alignment with current priorities. By examining collaboration patterns, researchers can identify potential collaborators, while understanding prevalent keywords enhances the visibility of their work. Additionally, bibliometric analysis highlights highly cited studies, guiding researchers to foundational literature relevant to their methodologies. Lastly, insights from these analyses can strengthen funding proposals by demonstrating alignment with trending topics and the potential impact of proposed research.

While our analysis provides valuable insights, it is essential to acknowledge certain limitations in the methodology. First, the reliance on the Web of Science database may introduce a degree of bias, as this platform primarily indexes literature from high-impact journals, which may overlook important studies published in less prominent venues. Additionally, non-English language publications were excluded from our analysis, which could result in the omission of relevant findings from regions where English is not the primary language of scientific communication. This limitation may have particularly affected research trends and perspectives from non-Western countries.

Bibliometric analysis is inherently influenced by the evolving nature of databases, as newly indexed articles and citation patterns can alter the findings over time. Future studies could benefit from integrating multiple databases to minimize potential bias and provide a more complete picture of the research landscape. Moreover, bibliometric analysis has inherent limitations. Highly cited papers may attract attention for reasons unrelated to scientific rigor, while significant studies in specialized fields may be under-cited. Citation practices can also be influenced by factors such as self-citations and access to open-source publications, potentially skewing the results.

Conclusion

Our study is the first to use bibliometric analysis to illustrate the current status and global trends of oliceridine research. Overall, oliceridine is in a phase of rapid development, indicating that this novel G-protein-biased μ-opioid receptor agonist has attracted widespread attention and become a hotspot in current research on pain treatment. However, to fully understand its therapeutic potential, more randomized controlled trials are needed, particularly in diverse patient populations beyond surgical settings. Continued research into the mechanisms and clinical applications of biased agonists will be crucial for advancing drug development and improving treatment outcomes in pain management.

Disclosure

The authors report no conflicts of interest in this work.

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