

# Shifting interpretations in evidence and guidance in pain and opioids research: A bibliometric analysis of a highly cited case series from 1986

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## Abstract

Rationale, aims, and objectives: Portenoy and Foley’s 1986 landmark study “Chronic use of opioid analgesics in non-malignant pain: report of 38 cases” has been reproached for opening the floodgates of opioid prescribing for chronic non-cancer pain and the attendant harms. This influential article has been cited over 500 times in the scientific literature over the last four decades. This study seeks to understand the impact of Portenoy and Foley’s article on subsequent discussions and research about opioids. Methods: We conducted a multi-method bibliometric analysis of all citations of this article from 1986 through 2019 using quantitative relational and qualitative content analysis to determine how uses and interpretations of this case series and associated prescribing guidance have changed over time, in relationship to the evolution of the North American opioid crises. Results: Using time series analysis, we identified three periods with distinct interpretations and uses of the index study. In the first “exploration” period (1986-1996), the index study was well-received by the scientific community and motivated further study of the effects of opioids. In the second “implementation” period (1997-2003, coinciding with the release of OxyContin®), this study was used as evidence to support widespread prescribing of opioid analgesics, even while it was recognized that long-term effects had not yet been evaluated. The third “reassessment” period (2004-2019) focused on how opioid-related harms had been overlooked, and in many cases these harms were directly attributed to this study. Conclusion: These changes in interpretation demonstrate shifting currents of the use and mobilization of evidence regarding pain and opioids, and how these currents both impact and are impacted by clinical practices and major sociohistorical phenomena such as the opioid crisis. Researchers and clinicians must account for these shifting dynamics when developing and interpreting scientific knowledge, including in the form of clinical practice guidelines.

Shifting interpretations in evidence and guidance in pain and opioids research: A bibliometric analysis of a highly cited case series from 1986

**Running Title:** Shifting interpretations in opioids research

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**Methods:** We conducted a multi-method bibliometric analysis of all citations of this article from 1986 through 2019 using quantitative relational and qualitative content analysis to determine how uses and interpretations of this case series and associated prescribing guidance have changed over time, in relationship to the evolution of the North American opioid crises.

**Results:** Using time series analysis, we identified three periods with distinct interpretations and uses of the index study. In the first “exploration” period (1986-1996), the index study was well-received by the scientific community and motivated further study of the effects of opioids. In the second “implementation” period (1997-2003, coinciding with the release of OxyContin®), this study was used as evidence to support widespread prescribing of opioid analgesics, even while it was recognized that long-term effects had not yet been evaluated. The third “reassessment” period (2004-2019) focused on how opioid-related harms had been overlooked, and in many cases these harms were directly attributed to this study.

**Conclusion:** These changes in interpretation demonstrate shifting currents of the use and mobilization of evidence regarding pain and opioids, and how these currents both impact and are impacted by clinical practices and major sociohistorical phenomena such as the opioid crisis. Researchers and clinicians must account for these shifting dynamics when developing and interpreting scientific knowledge, including in the form of clinical practice guidelines.

**Keywords:** Opioid Epidemic; Bibliometrics; Analgesics; Drug Prescriptions; Practice Patterns, Physicians’ (MeSH)

*Introduction:*

The over-prescribing of opioids for chronic non-cancer pain has played an important role in the development of the contemporary opioid crises in high-income North America.<sup>1-3</sup> In 2020, there were 6,214 and 81,000 opioid-related deaths in Canada<sup>4</sup> and the United States,<sup>5</sup> respectively. The combined costs of opioid use disorder and opioid overdoses in the United States were estimated to total USD 1.021 trillion in 2017 alone.<sup>6</sup> Historically, physicians had considered opioids to be effective and important treatments primarily for managing cancer pain. However, by the mid-1980s, scientific opinion started to shift towards considering the use of opioids to manage chronic non-cancer pain.<sup>7,8</sup> Many have pointed specifically to Portenoy and Foley’s 1986 article, “Chronic use of opioid analgesics in non-malignant pain: report of 38 cases”, as a seminal study that opened the door to mass opioid prescribing.<sup>2,3,9</sup>

Portenoy and Foley’s retrospective observational study of 38 patients fitting the criteria of having “non-malignant pain syndromes treated with opioid analgesics for at least 6 months” reported that only two patients - both with histories of substance abuse or mental illness - experienced management problems.

They therefore concluded that opioids could be “an alternative therapy which may be more humane and provide greater benefit at lesser risk than other approaches” for the treatment of chronic non-cancer pain.

While advocating for opioid prescribing to treat chronic pain, the 1986 study also presented opioid prescribing guidance. This included the tenet that “opioid maintenance therapy should be considered only after all reasonable attempts at pain management have failed.”<sup>10</sup>In many ways, the specifics of this guidance are similar to recent national guidelines published nearly four decades later in the United States<sup>11</sup>and Canada.<sup>12</sup>Even though the processes for producing these guidelines differed, they arrived at similar conclusions regarding prescribing opioids as a last resort, conducting risk-benefit analyses prior to prescribing, considering the importance of multidisciplinary care, and limiting doses.

Contemporary guidelines were developed as major clinical and policy responses to mass harms from opioids, while Portenoy and Foley’s guidance, despite its concordance with contemporary guidance, has been criticized as having initiated these very harms. This disconnect makes us reconsider the contemporary framing of the Portenoy and Foley article and raises important questions about how this paper has been cited, used, and interpreted over time.

Our primary objectives for this study were to explore the following questions:

What was the nature and magnitude of the impact of Portenoy and Foley’s 1986 article on the subsequent scientific literature?

How were Portenoy and Foley’s 1986 findings promoted, rejected, and constructed by the medical and scientific communities over time? What does this tell us about the evolution of pain and opioid prescribing research and practice?

This will provide insight not only into historical driving forces of the contemporary opioid crises, but also into historical and contemporary currents in clinical epidemiology and clinical medicine, including where the two are supposed to meet — in the realm of evidence-based practice.

### *Methods:*

A bibliometric analysis is well-suited to exploring our research questions. We used relational content analysis, supported by time series analysis and qualitative content analysis, to conduct a scientometric study<sup>13</sup>of all scientific citations of Portenoy and Foley’s 1986 article (the index study). The scientometric portion of our study aimed to quantitatively identify specific trends presented by the citing sources, allowing us to address our question regarding the impact of the 1986 study on subsequent scientific literature. We conducted a relational content analysis to synthesize quantitative and qualitative data, as well as to explore complex models in the development of historical scientific and medical thought.

### **Data sources**

We used the Web of Science Core Collection (WoS, by Clarivate Analytics) to collect all studies that cited the index study. WoS is commonly used for bibliometric analyses,<sup>14</sup>and we chose this database over alternatives such as Scopus and Google Scholar because of the availability of detailed citation metadata such as research areas, article type, funding agencies, and countries of origin. We conducted a search in June 2019 and then an update in July 2020 covering the period from the publication of the index study through to the end of 2019. The citation information for every article was collected into EndNote (by Clarivate Analytics), which was used to retrieve full text records. The remaining full text records were retrieved manually. We examined all the retrieved full text articles to ensure that the index study was indeed cited. Metadata collected from WoS were collected and managed using Microsoft Excel (by Microsoft).

### **Outcome measures**

#### *Content analysis*

After collecting all of the citing sources, we conducted a relational content analysis<sup>15</sup>that explored the relationship between Portenoy and Foley’s 1986 article and each of the citing works. While similar studies

have focused on whether citations were affirmative or negative,<sup>16</sup> we expanded the scope of our study to construct a more detailed analysis of the citation patterns in the scientific literature. We identified five relevant outcomes: sign (affirmational, negational, or neutral reference), accuracy of index study citation, attribution of the index citation to driving the opioid crisis, agenda-setting, and article type (Table 1).

<Table 1. Description and Definition of each outcome>

### Data collection and analysis

Three authors (A.S., S.T., and A. Su.) first conducted a calibration exercise with 50 randomly selected records. We reviewed our categorizations and identified any areas of disagreement to refine our coding process. Then two authors (A.S. and S.T.) independently and in duplicate assessed and categorized each citation against the index citation using the definition of each outcome. These categorizations were reconciled and any conflicts were discussed with a third author (A. Su.). Metadata were also collected directly from WoS. These included research area, article type, country of origin, and funding sources for each article.

Proportions between categories were compared using Chi-squared or Fisher Exact tests. All tests were two sided and  $p < 0.05$  was considered statistically significant.

### *Time-Series Analysis*

Similar to the procedure of a recent analysis,<sup>17</sup> we then conducted time-series analyses to explore any time-based trends in the number of articles published per year for each coded category.

A preliminary visual inspection of all the time-series plots identified outstanding trends for further investigation. We used the Chow test to test for the presence of structural break points in time series data.<sup>18</sup> Segmented regression of interrupted time series analysis with AR(2) residuals were used to examine the sudden and gradual change in the proportions of publications of interest at given time points.<sup>19</sup>

### *Qualitative Analysis*

Finally, the content and time-series analyses were supplemented by a qualitative analysis. We noted a clear time-based trend in the publication of citing articles in the anaesthesia field, which had three publication peaks that stood out from the other research areas. We purposively sampled all the articles from this field that were published in each of the three peaks through the study period. These papers were re-read and analyzed with a focus on the larger context of the citation of the index study, as well as the general tone of the article towards opioids and opioid prescribing for chronic non-cancer pain. Once each paper was analyzed, attitudes towards opioid prescribing were summarized for each peak year. These summaries were then compared to the quantitative results in order to add depth and context to our overall findings.

### *Results:*

In total, 523 articles were identified through WoS through the end of 2019, placing it in the 99.8th percentile of all scientific publications in the WoS categories of anesthesiology, neurosciences, clinical neurology, general & internal medicine from 1986. Five hundred and eleven (97.7%) full text records were included in the analysis (Figure 1). The remaining 12 were either unretrievable ( $n=8$ ), or were erroneously identified by WoS as citing the index study ( $n=4$ ). The reviewers assessed English, French, and German articles in the original language. Three other articles that were published in Polish, Portuguese, and Spanish were reviewed using Google Translate, an online translation software (by Google).

<Figure 1. Time series of citing papers published from 1986-2019>

### **Time-Series Analysis:**

On visual inspection of the time-based distribution of each of the outcomes (Supplementary File 1), we identified possibly significant time-based trends only in the sign and attribution outcomes. Piecewise linear regression of the sign and attribution time series identified two definitive breakpoints that were consistent across both outcomes (Figure 2).

<Figure 2. Piecewise linear regression of the sign and attribution time-series for citing papers published from 1986-2019 >

For affirmational and neutral citations, a breakpoint was identified in 1996, after which the rate decreased significantly (Figure 2a). Non-attributive citations also had a breakpoint in 1996 (Figure 2b).

The time-series analysis for negational citations identified a significant breakpoint in 2004 (Figure 2a). Following that year, the number of negational citations substantially increased. Similarly, the time-series analysis for citations that attribute the opioid crisis to Portenoy's paper had a distinctive breakpoint in 2004 (Figure 2b). After 2004, many more papers cited Portenoy's paper as a motivating factor behind the opioid crisis.

### Categorical Analysis:

Given these two breakpoints, and our two endpoints of 1986 and 2019, we categorized the data into three time-based groups: 1986-1996, 1997-2003, and 2004-2019 (Table 2).

Overall, the largest proportion of citations were neutral (45.4%). The majority were accurate (78.9%), non-attributive (78.3%), non-agenda-setting (59.9%), and non-empirical articles (57.7%). Moreover, the majority of articles were published in the U.S. and Canada (69.7%). Articles were published in a wide range of research areas, although papers were concentrated within the areas of neurosciences & neurology (22.6%) anesthesiology (16.2%), and general & internal medicine (15.3%).

<Table 2. Categorical Bibliometric Data Across the Three Time Periods>

#### *Sign*

Categorically, there was a substantial and continuous decrease in affirmational citations over the three periods (50.4% to 38.6% to 25.4%). The decrease in affirmation from the first to the second periods was driven by an increase in neutral articles while the decrease in affirmation from the second to the third periods was driven by an increase in negational articles. Agenda-setting was significantly higher in negational (41.6%) and neutral (48.3%) articles than affirmational (28.7%) articles (Supplementary File 2).

#### *Accuracy*

There was a consistent decrease in accuracy over the three periods (88.2% to 80.0% to 73.8%). There was also a consistent increase in inaccurate citations over these periods (8.4% to 13.6% to 20.2%).

#### *Attribution*

There were no attributional articles in the 1986-1996 period and very few (0.7%) in the 1997-2003 period (Fig. 2b). There was a large spike in attributional articles in the 2004-2019 period (43.7%). Negational articles (54.5%) had the highest proportion of attribution, followed by neutral (23.3%), and affirmational (1.1%) articles.

#### *Agenda-setting*

The proportion of agenda-setting articles remained relatively constant throughout the period of analysis (38.7% to 36.4% to 42.9%). However, over the three time periods, there was a reversal of the dominant sign of the agenda-setting citations. In the first period, agenda-setting citations were significantly more affirmational (37.0%) than negational (6.5%), while in the third period, they were increasingly negational (34.3%) and less affirmational (17.6%) (Supplementary File 2).

#### *Article type*

The proportion of empirical articles peaked in the second period before decreasing (from 47.1% to 32.1%) in the third period. Affirmational non-empirical articles (53.6%) were higher in proportion than affirmational empirical articles (46.0%) in the first period. However, this difference was reversed in the third period, where affirmational empirical articles (29.6%) were higher in proportion than affirmational non-empirical articles

(23.4%), (Supplemental digital content 1). Empirical articles (52.9%) were significantly more agenda-setting than non-empirical articles (31.5%) throughout all three periods.

### *Research area, country of origin, and funding source*

The proportion of neurosciences & neurology and pharmacology & pharmacy articles decreased over time. Substance abuse articles were uncommon in the first two periods before spiking in the third period. The other research areas did not show a clear trend over the three time periods. In all three periods, more papers were published in the US and Canada than in the rest of the world. The proportion of papers published in the US and Canada stayed relatively constant in the first two periods before spiking in the third period. Most citing papers (79%) had no disclosed funding source. The largest funder of research was the National Institute on Drug Abuse, which funded 35% of citing articles with known funding sources.

### **Qualitative Analysis:**

Amongst the anaesthesia papers, we identified three distinctive peaks that aligned with the middle of each of our three identified time categories (Figure 3). We qualitatively assessed the six, seven and eight anaesthesia papers that were published during the peak years of 1991, 2000, and 2010, respectively.

<Figure 3. Citing anesthesiology papers published from 1986-2019>

#### *Sample 1: 1991*

Almost all papers published in 1991 acknowledged the controversy surrounding opioid prescribing and expressed concern at the lack of definitive scientific evidence about the long-term impacts of opioid use.<sup>20–25</sup> Most of these articles were empirical trials (66.7%), half of which were animal-based. The authors expressed an interest in trying to better understand pain and pain prevention. These articles generally cited the index paper's findings as a motivating reason for their early-stage research.

Even though there were concerns about the lack of scientific evidence in 1991 for opioid prescribing, the majority of authors cited the index study neutrally or affirmatively. This is exemplified by Brena, who concludes that “[at] the present level of information, a prudent and unbiased course of action is mandatory. We must limit and resist the use of opioids in non-malignant pain at the clinical level until cross-validated empirical answers . . . are available.”<sup>21</sup>

#### *Sample 2: 2000*

Papers published in 2000<sup>26–32</sup> generally acknowledged concerns about opioid prescribing, but viewed them as a secondary concern after treating pain. For example, Quang-Cantagrel writes that the controversy about opioids “results from confusion about pathologies which could benefit from opioids and misconceptions about addiction and tolerance that may result from long-term opioid administration.”<sup>30</sup> Similarly, Watson acknowledges that “the use of opioids for neuropathic pain, generally when all else has failed, remains contentious,” but immediately goes on to write that “opioids may be the only avenue of relief for many patients with severe neuropathic pain.”<sup>32</sup>

Anesthesiology articles published in 2000 were more supportive of opioids for pain treatment (57.1%) than they were in 1991. There was common agreement that opioids can be safe and effective for short-term treatment of non-cancer pain. Yet, there continued to be uncertainty and disagreement about long-term effectiveness and risks of opioid treatment for chronic pain. Covington writes that “[w]hat we do not yet know is what the effects will be of years, in fact decades, of opioid treatment of intractable pain.”<sup>27</sup> Only Mindach took a strong stance against the index study and opioid prescribing in his commentary, claiming that “[n]ot a single convincing clinical study could be found to prove the claimed absence of addiction in pain patients.”<sup>29</sup> Of note, this article was published in a German, rather than an American or Canadian, journal.

#### *Sample 3: 2010*

Anesthesiology papers published in 2010<sup>33–40</sup> expressed increasing skepticism about the effects of long-term opioid prescribing and began documenting opioid-related harms. Most papers did not necessarily report that

opioids were ineffective for pain relief. Instead, they pointed out that other negative consequences have been overlooked. A study of patients who received opioids for chronic non-cancer pain concluded “that the range of possible harms from [chronic opioid therapy] may be broader and of a different nature than has been described in treatment guidelines.”<sup>40</sup> This is a widely shared sentiment in most of the articles in this sample. For example, Jay writes that “[t]he treatment of the CNCP patient with only narcotics is problematic and most often leads to failure. The most appropriate treatment is within an inter-disciplinary pain management program.”<sup>34</sup> This represents a significant change in the tone of anesthesiology papers from 2000, when opioid prescribing was generally advocated as a standalone solution for chronic non-cancer pain.

*Discussion:*

## Summary of findings

Portenoy and Foley’s study has been cited more than 500 times, placing it amongst the most commonly cited articles from 1986. These citations have not only been sustained over a period of four decades, but the annual number of citations has continued to increase in recent years demonstrating the continued and profound impact of this article on pain- and opioid-related scholarship and practice. Besides these gross measures of impact, we identified three distinct periods in which the index study was interpreted and used by the scientific and clinical communities. Building on Geels’ sociotechnical analysis of the societal embedding of psychotropic medications,<sup>41</sup> we can frame these three periods more specifically as waves of *exploration*, *implementation*, and *reassessment* (Table 3). This framing emphasizes the importance of sociohistorical context in determining how the index study has been interpreted. An understanding of this process is important to both practitioners and researchers as we attempt to interpret scientific evidence to best inform prescribing practices and research agendas.

<Table 3. Summary of Findings by Period >

Citing articles from the first period (1986-1996) expressed concern at the lack of scientific evidence for long-term opioid prescribing. The articles published in this period were more accurate and affirmational than the two subsequent periods. Compared to later interpretations of the index study, these more accurately represented the actual conclusions and prescribing guidance proposed by Portenoy and Foley. This was a period of *exploration* with a focus on increasing the amount of evidence for opioid prescribing for chronic non-cancer pain.

However, this period of exploration concluded at our identified breakpoint in 1997. Just a year before, OxyContin® was approved in the United States, a drug that would go on to define the early American opioid crisis. What had been a period of exploration quickly transitioned into a period of *implementation* during which sales of OxyContin® skyrocketed from \$48M USD in 1996 to \$1.1B in 2000.<sup>42</sup> In this second period (1997-2003), the proportion of empirical articles reached its highest peak of the three periods. At first glance, this signifies that concerns about the need for more scientific evidence for opioids from the first period were being addressed. However, our qualitative analysis suggests that this empirical research focused mostly on the efficacy of short-term opioid use, rather than providing details about long-term effects, either negative or positive. This was coupled with a rise in inaccurate citations demonstrating that interpretations began to stray further from the substance of the index study. In the first *exploration* period, the index study was being accurately cited as impetus to seek more evidence for opioid prescribing, but by this second *implementation* period it was increasingly being inaccurately cited as evidence in support of regular opioid prescribing.

In other words, a push for increased opioid prescribing altered how scientific evidence was interpreted. In their analysis on the societal embedding of new technologies, Geels et al. write that “innovators, entrepreneurs or health advocates try to attract attention from sponsors and lobby to create a favourable regulatory environment. Product champions make optimistic, but diffuse promises about future performance, societal benefits and profits.”<sup>41</sup> In this case, the index study was used to make “diffuse promises” that in many cases were inaccurate. This misinterpretation is most obvious in how the index study’s recommendation of interdisciplinary treatment was largely overlooked. While Portenoy and Foley originally noted that opioids should be prescribed as part of an interdisciplinary treatment plan with the “concurrent use of ancillary cognitive/behavioural

and physical therapies,” the promised benefits of opioids quickly overshadowed this recommendation. According to Bernard et al., “what was intended to be multimodal care, however, became unidimensional care in most settings with reliance almost completely on pharmacologic solutions to pain.”<sup>43</sup> The prospect of opioids as a one-step solution for chronic pain prompted governmental and non-governmental organizations to make opioids more accessible for chronic non-cancer pain.<sup>43</sup> This second period showed an increasingly liberal and often inaccurate interpretation that was associated with increasing opioid-related harms.

Between 2004 and 2019, opioid-related harms increasingly permeated North American society. Whereas the previous periods explored and implemented opioids as a solution for chronic pain, this latter period has been one of concern and *reassessment*. The number of papers that attributed the opioid crisis to the index study grew exponentially. Negative citations also grew significantly, making this by far the most negational period. As opioids drew more ire from the scientific community, so too did the index study. This tracks with Geels’ model that the “peak of inflated expectations” is often followed by a trough of disillusionment in which “there are some successes with the new technology, but more failures.”<sup>41</sup> This process is exemplified by yet another rise in inaccurate citations in the third period. However, these now grew alongside attributive and negational citations. Whereas earlier inaccurate citations were affirmational and encouraged liberal opioid prescribing practices, these later inaccurate citations were negational and misinterpreted the index study as having been a *carte blanche* for opioid prescribing that incited the crisis.

## Implications

The timeline periods identified in this study accord strongly with other studies which have demonstrated three phases of scientific communication relating to opioid dose reduction and multidisciplinary care<sup>17</sup> and even mass media coverage of the opioid crisis.<sup>44</sup> The former study specifically identified a cross-correlation with a two-year lag between opioid overdose deaths in the US and scientific communication about opioids, clearly identifying a two-way, push-pull relationship between clinical science and the opioid crisis, a major sociohistorical phenomenon. These studies have collectively identified the 2004 moment as a major inflection point in perceptions and activity relating to opioid-related harms, but at the same time have identified that this inflection is tied directly to shifting norms and forces building over the preceding two decades.

Besides communicating outcomes of a series of cases related to opioid prescribing, Foley and Portenoy’s article also included substantive clinical guidance for opioid prescribing for non-cancer pain. By contemporary standards of evidence-based medicine, this guidance can certainly be criticized regarding both the quality of the underlying evidence but also on the opaque and likely idiosyncratic process through which this guidance was developed. Yet, in the specifics of its content, this guidance very much accords with contemporary clinical practice guidelines for opioid prescribing, most of which were developed as responses to overprescribing and its attendant harms.<sup>11,12</sup> We see here the dual possibilities outlined by Timmermans and Berg<sup>45</sup> of similar clinical guidance being used to stake out new professional territory and expand medical autonomy in the period of expansion in the mid-1980s versus holding physicians accountable for their practices during our contemporary period of reassessment (2004-2019). Rather than attending to guidance content alone or even the processes of developing guidance,<sup>46</sup> this concordance draws our attention back to the importance of sociohistorical context in determining how clinical guidance is interpreted and utilized within health systems, and thus influencing the ultimate impacts of this guidance. As the challenges with the implementation of contemporary guidelines have emphasized,<sup>47,48</sup> understanding and accounting for this contextual effect is a major challenge for future clinical practice guidance in the complex area of opioid prescribing. Indeed, a plurality of scientific approaches and perspectives are needed to provide appropriate, context-sensitive guidance for clinicians and policy-makers.<sup>49-51</sup> These are particularly relevant in this therapeutic area of opioid prescribing where processes for developing revised clinical practice guidelines are currently underway.<sup>52</sup>

## Strengths

To our knowledge, this is the first systematic study of the effects of Portenoy and Foley’s seminal 1986 article. By analyzing 511 full-text citing articles, this study paints a detailed picture of the substantial and ongoing scientific impact of the index study. We analyzed all identified and retrievable articles regardless



of country of origin or language of publication allowing us to establish a global, rather than only North American, understanding of the index study's impact. Finally, this study uniquely combined bibliometrics, time-series analyses, relational content analysis, and qualitative analysis. These multiple analyses demonstrate strong concordance and thus strengthen our confidence in the findings, and provide a deeper and broader understanding of the evolution of opioid-related research between 1986 and 2019.

## Limitations

The index study is only one of several seminal articles discussing opioid treatment for chronic non-cancer pain that preceded the opioid crisis. Therefore, our study does not capture the entire picture of interpretations and reinterpretations of scientific knowledge concurrently with the dynamics of the opioid crisis. Similar examinations of other seminal articles would provide a more comprehensive view. Furthermore, citing articles were only collected from WoS. While this database is commonly used for bibliometric analyses, a similar study using other databases such as Scopus or Google Scholar may have yielded different outcomes and thus alternative conclusions.

The coding of the citing articles would be subject to the biases and idiosyncratic interpretations of the reviewers. We aimed to mitigate these effects by using clear coding schema and coding independently and in duplicate. However, there is still the possibility of the coding procedure introducing unknown biases to this study.

## Conclusion:

This systematic analysis of 511 articles citing Portenoy and Foley's 1986 study demonstrates the winding evolution of its interpretation and related impact on pain and opioid scholarship. A time-series analysis identified three distinct periods of interpretation of the index study which we labelled as periods of exploration, implementation, and reassessment. These periods of interpretation align well with inflection points identified by other studies and with major sociohistorical phenomena related to pain management and opioid prescribing. This illustrates both the fluidity of scientific interpretation in pain medicine and research, and the importance of sociohistorical context to this interpretation. Practitioners and researchers should be attuned to this shifting nature of interpretation to better develop, critically evaluate, and apply scientific knowledge.

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**Table 1: *Description and Definition of each outcome***

Variable	Description
<b>Sign</b>	Identified whether the citing article affirmatively, negatively, or neutrally referred to the index study..
<b>Accuracy</b>	Similar to past studies that categorized textual evidence in order to examine varying perspectives in ar
<b>Attribution</b>	Assessed the perceived impact by the scientific community of the index study on opioid prescribing pra
<b>Agenda Setting</b>	Whether the index study was fundamental to the motivation or design of the study at hand <sup>54</sup> .
<b>Article Type</b>	Identified the citing article as either empirical or non-empirical research.

*Description of sign, accuracy, attribution, agenda setting, and article type along with a definition of each of their respective outcomes. The definitions were used as guides to code each article in the relational content analysis.*

**Table 2: *Categorical Bibliometric Data Across the Three Time Periods***

Variable	Outcome	Total (%)	Number (%)	Period 1 1986-1996	Number (%)
<b>Sign</b>	Affirmation	178 (34.8)	60 (50.4)		54 (38.6)
	Negation	101 (19.8)	6 (5)		10 (7.1)
	Neutral	232 (45.4)	53 (44.5)		76 (54.3)
<b>Accuracy</b>	Accurate	403 (78.9)	105 (88.2)		112 (80)
	Inaccurate	80 (15.7)	10 (8.4)		19 (13.6)
	Neither	28 (5.5)	4 (3.4)		9 (6.4)
<b>Attribution</b>	Attributed	111 (21.7)	0 (0)		1 (0.7)

<b>Agenda Setting</b>	Not attributed	400 (78.3)	119 (100)	139 (99.3)
	Agenda setting	205 (40.1)	46 (38.7)	51 (36.4)
<b>Article Type</b>	Not agenda setting	306 (59.9)	73 (61.3)	89 (63.6)
	Empirical Research	197 (38.5)	50 (42)	66 (47.1)
<b>Research Area</b>	Non-Empirical Research	314 (61.5)	69 (58)	74 (52.9)
	Neurosciences & Neurology	179 (22.6)	48 (27.1)	55 (24.2)
	Anesthesiology	128 (16.2)	24 (13.6)	44 (19.4)
	General & Internal Medicine	121 (15.3)	24 (13.6)	36 (15.9)
	Pharmacology & Pharmacy	56 (7.1)	18 (10.2)	18 (7.9)
	Psychiatry	39 (4.9)	4 (2.3)	13 (5.7)
	Health Care Sciences & Services	36 (4.6)	9 (5.1)	10 (4.4)
	Substance Abuse	21 (2.7)	3 (1.7)	2 (0.9)
	Psychology	19 (2.4)	6 (3.4)	4 (1.8)
	Surgery	14 (1.8)	1 (0.6)	4 (1.8)
	Other	179 (22.6)	40 (22.6)	41 (18.1)
<b>Country of Origin</b>	USA & Canada	371 (69.7)	75 (62)	86 (58.9)
	Rest of the world	161 (30.3)	46 (38)	60 (41.1)

*Categorical bibliometric data for sign, accuracy, attribution, agenda-setting, article type, research area, and country of origin. Overall data and data by each of three Periods are displayed.*

**Table 3: Summary of Findings by Period**

Characteristic	Period of Exploration (1986-1996)
<b>Dominant sign toward the index study</b>	Affirmation
<b>Attribution of the index study to the opioid crisis</b>	Not attributed
<b>Concern toward opioid risks</b>	Acknowledges the lack of scientific evidence on the long-term effects of opioids
<b>Motivation of research</b>	Better understand the benefits and risks of opioids

*Description of the main characteristics of each time period identified via quantitative and qualitative analyses, including the dominant sign toward index study, attribution of the index study to the opioid crisis, concern toward opioid risks, and motivation of research.*

*Figure Titles and Legends:*

Figure 1. Number of citing papers published from 1986-2019

*A time series illustrating the annual number of citations of the index study between 1986 and 2019.*

Figure 2. Time-series for citing papers published from 1986-2019

*Two piecewise linear regressions with smoothed curves of time-series for sign and attribution outcomes, demonstrating concordant breakpoints in 1996 and 2004.*

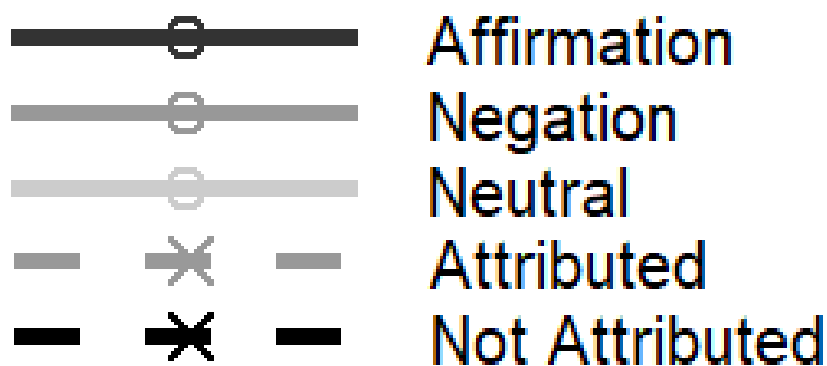


Figure 3. Citing anesthesiology papers published from 1986-2019

*A time series illustrating the annual number of citing anesthesiology papers published between 1986 and 2019. The “sign” of the citations is shown for the three years of interest: 1991, 2000, and 2010.*



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