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REVIEW ARTICLE

# Quality of Cancer Pain Management: An Update of a Systematic Review of Undertreatment of Patients With Cancer

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## ABSTRACT

### Purpose
Pain is a frequent symptom in patients with cancer, with substantial impact. Despite the availability of opioids and updated guidelines from reliable leading societies, undertreatment is still frequent.

### Methods
We updated a systematic review published in 2008, which showed that according to the Pain Management Index (PMI), 43.4% of patients with cancer were undertreated. This review included observational and experimental studies reporting negative PMI scores for adults with cancer and pain published from 2007 to 2013 and retrieved through MEDLINE, Embase, and Google Scholar. To detect any temporal trend and identify potential determinants of undertreatment, we compared articles published before and after 2007 with univariable, multivariable, and sensitivity analyses.

### Results
In the new set of 20 articles published from 2007 to 2013, there was a decrease in undertreatment of approximately 25% (from 43.4 to 31.8%). In the whole sample, the proportion of undertreated patients fell from 2007 to 2013, and an association was confirmed between negative PMI score, economic level, and nonspecific setting for cancer pain. Sensitivity analysis confirmed the robustness of results.

### Conclusion
Analysis of 46 articles published from 1994 to 2013 using the PMI to assess the adequacy of analgesic therapy suggests the quality of pharmacologic pain management has improved. However, approximately one third of patients still do not receive pain medication proportional to their pain intensity.

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## INTRODUCTION

Pain is a frequent, burdensome symptom in patients with cancer. The prevalence rate estimated from a systematic review including articles published over a period of 40 years is higher than 50%, with variability according to type of cancer (52% to 70%), disease stage (55% to 64%), and aim of anticancer treatment (33% to 59%).[1] High prevalence has also been documented in hematologic patients at diagnosis, during therapy, and in the last month of life.[2,3] Effective analgesic therapy based on opioids, as suggested by several guidelines, including the well-known WHO recommendations[4] and the more recent recommendations from the European Association for Palliative Care[5] and the European Society of Medical Oncology,[6] is potentially effective in most cases.[7] However, undertreatment is amply documented.[8,9]

A systematic review covering 26 studies from 1994 up to 2007 that adopted the Pain Management Index (PMI) to assess the adequacy of pharmacologic pain therapy reported the rate of potentially undertreated patient cases from 8% to 82%, with a weighted mean of 43%,[10] although more recent studies seem to suggest lower levels of inappropriate analgesic care.[11-14] Therefore, it might be expected that in the last few years, the quality of cancer pain management has improved. However, because differences in study design and setting do not permit any solid conclusion, a formal evidence-synthesis process is recommended to investigate any possible time trend.

We updated the previously systematic review[10] to assess whether any change could be detected in

the quality of pain management in adults with cancer, in terms of adequacy of analgesic prescription. In this article, we describe the studies published after 2007, compare the undertreatment estimates before and after 2007, assess the temporal trend from 1994 to 2013 in the whole sample of studies, and identify variables associated with undertreatment using a set of potential determinants.

## METHODS

### Selection of Studies and Their Main Characteristics

We included the articles analyzed in the previous review[10] and updated the sample through a MEDLINE and Embase search from November 2007 to September 2013. A further search was done using Google Scholar, and cancer pain treatment experts were asked to report any additional articles about undertreatment.

The literature search used the same strategy as in the previous review[10] (ie, pain management AND index OR measure). Only articles in English involving human adults were considered. Two investigators (M.T.G. and A.R.) independently reviewed titles and abstracts, selecting articles reporting the prevalence of undertreatment in adult patients with cancer, defined as the proportion of patients in each study with a negative PMI score. Disagreements were solved by discussion and consensus.

We selected the final sample according to the following criteria: original studies; patients with cancer; and PMI score for each patient and the percentage of negative PMI scores in the study. Both observational and experimental studies were included. All types of PMIs (ie, Zelman et al,[15] Ward et al,[16] and Cleeland[9]) were included in the search, but only articles using the PMI by Cleeland, defined as "an index that subtracts the patient's rating of pain from the rating of the strongest analgesic agent,"[9(p393)] were included in this analysis (Appendix, online only).

The following study characteristics were recorded on a data extraction sheet developed with a pilot-tested procedure: country, aim of the study (prevalence of undertreatment or others), setting, sample size, participant characteristics (age, percentage of men, type of cancer, presence of metastasis), and percentage of negative PMI scores. The predictor variables considered in the previous review were tested:

*Setting.* In the previous review, this was classified as specific for patients with cancer, nonspecific, or mixed (hospice and oncologic ward were specific, whereas general wards and general practice were nonspecific). In this study, we classified the setting as specific for cancer pain and nonspecific, so hospices, cancer pain centers, palliative care centers, or oncologic wards were specific, and general wards were nonspecific. For multicenter studies involving specific and nonspecific settings for cancer pain, the setting was considered mixed.

*Country economic level.* The previous review estimated this using the gross national income (per capita) converted to US dollars following the World Bank Atlas method, divided by the midyear population.[17] For this review, we applied the international human development indicators (IHDIs),[18] and for each article (both old and new), we reported the gross national income per capita in purchasing power parity terms for the year of publication of the study. We then classified the country variable for each study into four categories (very high, high, medium, and low human development) according to the IHDI cutoffs and used these as a proxy for the economic level. The low and medium levels were merged to produce more comparable groups in terms of size.

*Year of publication.* This was considered a proxy of the year of study conduction, because several articles did not report this information.

*Geographic areas.* Areas included Europe, North America, Asia, Africa, and Australia.

*Stage of disease.* We used the percentages of patients in the sample of each article with metastatic or advanced disease, when reported, and took adopting the mean (68.8%) as a cutoff for classification, as in the previous review.

*Age.* We took the mean age of the sample for each article (median when average age was not specified) and adopted the median across articles (62 years) as a cutoff for classification.

### Quality Assessment

Articles were evaluated using the methodologic quality criteria for prevalence studies developed by Leboeuf-Yde and Lauritsen[19] and Walker,[20] later adapted to cancer pain by van den Beuken-van Everdingen et al[1] and Deandrea et al.[21] For the current analysis, questions targeted to cancer pain were replaced with PMI questions (Appendix Table A1, online only). This resulted in quality scores from 0 to 19 points for studies where all the criteria were applicable and from 0 to 15 when some were not applicable. The quality assessment was entered as an explanatory variable in the regression analysis and was also used in the sensitivity analysis.

### Statistical Analysis

The range of negative PMI percentages, standard deviations, medians, and means weighted by sample size for the whole study pool and for subgroups described were computed. The *t* test for two independent samples was used to compare the percentages of negative PMI scores weighted by the sample size for subgroups, for the years 1994 to 2000 versus the years 2008 to 2013. A *P* value less than .05 was considered statistically significant.

In the whole sample of studies published from 1994 to 2013, univariable regression analysis was used to describe the relationship between the response variable (percentage of PMI scores as continuous variable) and the year of study publication as continuous variable. In the same sample, multivariable regression analysis was used to describe the relationship between the response variable (percentage of PMI as continuous variable) and a list of potential explanatory variables (setting of care, economic level of country, size of study, patient age, year of publication, and quality score). All the explanatory variables were considered as continuous, except for age, which was classified according to the median (62 years). To reduce the regression mean square error, sample size was included among the explanatory variables, because visual inspection indicated some degree of correlation. Each variable was controlled for all the others in the model.

## RESULTS

The search of MEDLINE and Embase from November 2007 to September 2013 produced 2,806 citations, and five additional cases were identified through Google Scholar or from experts in the field. After removing duplicates, 2,697 records remained. Of these, 2,670 were discarded, because after reviewing the abstracts, they did not meet the inclusion criteria. The full text of the remaining 27 was examined, and seven articles were excluded as not regarding cancer pain. The 20 studies[12,13,22-39] that met the inclusion criteria and were included in the current analysis are listed in Table 1. The flowchart of study selection is shown in Figure 1.

Table 2 lists selected characteristics of the 46 studies from 1994 to 2013. A comparison of the two sets of studies suggests that those published after 2008 had a somewhat lower prevalence of undertreatment; in fact, the negative PMI scores ranged from 8% to 82% to 4% to 68%, the median from 60% to 37.1%, and the weighted mean from 41.5% to 31.8%. The Asia group reported the highest rate of negative PMI scores from 1997 to 2007 (59.1%); the Africa group did so from 2008 to 2013 (63.1%). Patients with less advanced disease seemed to be more undertreated as well (1994 to 2007, 58.4%; 2008 to 2013, 37.8%). The distributions of undertreatment also differed for the setting of care. From 1994 to 2007, the nonspecific setting had the lowest negative PMI scores, whereas in more recent years, specific or mixed centers for cancer pain had lower percentages of negative PMI scores.

  

**Table 1.** Details of 20 Original Studies Reporting Cleeland[9] PMI Scores

| Study | Year of Publication | Country/Region | No. of Patients | Setting | Negative PMI Scores | | Quality Score (%) |
|---|---|---|---|---|---|---|---|
| | | | | | % | 95% CI | |
| van den Beuken-van Everdingen et al[33] | 2007 | Netherlands | 1,429 | Mixed | 42.0 | 39.44 to 44.56 | 79 |
| Donovan et al[23] | 2008 | North America | 131 | Specific | 46.5 | 37.96 to 55.04 | 100 |
| Kalyadina et al[26] | 2008 | Russia | 120 | Specific | 68.0 | 59.65 to 76.35 | 79 |
| Shen et al[29] | 2008 | China | 304 | Specific | 60.2 | 54.70 to 65.70 | 74 |
| Torvik et al[32] | 2008 | Norway | 79 | Specific | 10.0 | 3.38 to 16.62 | 63 |
| Apolone et al[22] | 2009 | Italy | 1,801 | Specific | 25.3 | 23.29 to 27.31 | 100 |
| Gagliese et al[25] | 2009 | Canada | 32 | Specific | 34.4 | 17.94 to 50.86 | 93 |
| Fan et al[24] | 2010 | Asia | 98 | Specific | 39.8 | 30.11 to 49.49 | 40 |
| Lovell et al[27] | 2010 | Australia | 158 | Specific | 20.2 | 13.94 to 26.46 | 74 |
| Mitera et al[28] | 2010 | Canada | 2,011 | Specific | 25.1 | 23.20 to 27.00 | 100 |
| Mitera et al[13] | 2010 | Canada | 1,000 | Specific | 25.8 | 23.09 to 28.51 | 100 |
| Sichetti et al[30] | 2010 | Italy | 819 | Mixed | 14.9 | 12.46 to 17.34 | 93 |
| Fisch et al[12] | 2012 | North America | 2,026 | Specific | 41.0 | 38.86 to 43.14 | 80 |
| Makama et al[34] | 2012 | Nigeria | 58 | Nonspecific | 63.1 | 50.68 to 75.52 | 67 |
| Tateno et al[31] | 2012 | Japan | 24 | Specific | 41.7 | 21.97 to 61.43 | 73 |
| Yen et al[35] | 2012 | United Kingdom | 57 | Specific | 63 | 50.47 to 75.53 | 87 |
| Gonçalves et al[36] | 2013 | Europe | 136 | Specific | 4 | 0.71 to 7.29 | 87 |
| Kwon et al[37] | 2013 | Asia | 201 | Specific | 12 | 7.46 to 16.42 | 60 |
| Mercadante et al[39] | 2013 | Europe | 167 | Specific | 26 | 19.12 to 32.38 | 67 |
| Te Boveldt et al[38] | 2013 | Europe | 129 | Specific | 62 | 53.64 to 70.39 | 87 |

Abbreviation: PMI, Pain Management Index.

The median study quality for the 26 studies from 1994 to 2007 was 0.80; for 2008 to 2013, it was 0.79.

The proportion of patients classified as undertreated according to year of study publication (Appendix Fig A1, online only) shows a linear trend. Articles published more recently showed a tendency toward a lower prevalence of undertreatment. Univariable regression showed a decrease in undertreatment of approximately 1 point per year (95% CI, −2.16 to 0.15; $P = .09$), which corresponds to a 5% decrease every 5 years in the proportion of patients classified as undertreated according to the PMI. This was more evident when articles were grouped into three categories by year of publication; the decrease in undertreatment was substantial over the years, with a change of 32% ($P < .001$) when articles published from 2008 to 2013 were compared with those published from 1994 to 2000 (Table 3). A weak nonstatistically significant linear trend was observed ($r = 0.13$; $P = .39$; Appendix Fig A2, online only) in the quality score level in relation to year of publication from 1994 to 2013.

When the relation between PMI score and time was further explored in a multivariable analysis controlling for setting, size of study, mean age of patients, quality score, and economic level of the country, the decrease in undertreatment for each year was still approximately 1 point (95% CI, −2.38 to 0.34; $P = .14$; Table 4). Setting (nonspecific) and (lower) economic level were the only variables with an important significant association with PMI score.

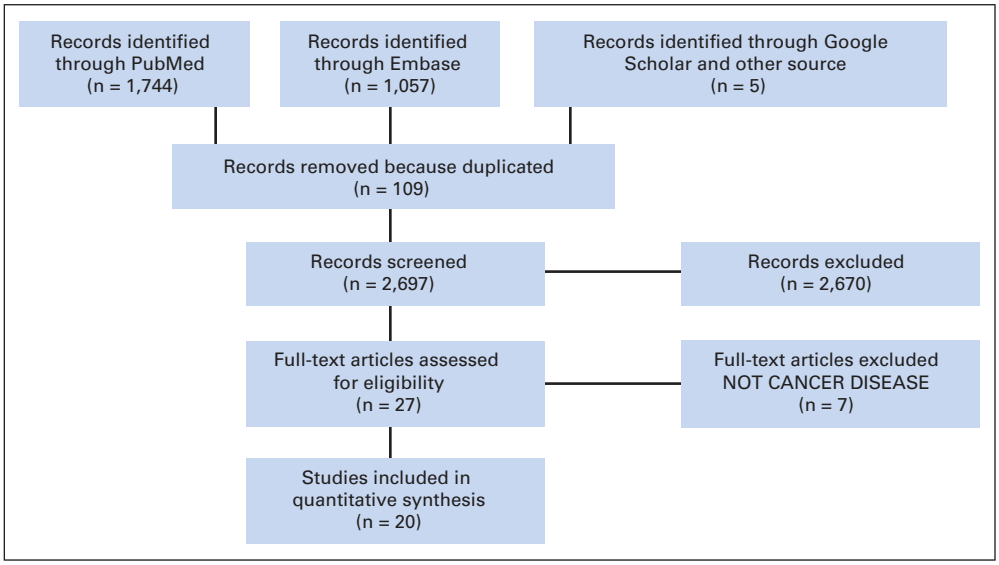


**Fig 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

**Table 2.** Selected Characteristics of 46 Original Studies Reporting PMI Estimates

| Characteristic | Articles From 1994 to 2007 | | | | | Articles From 2008 to 2013 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Studies | Range of Negative PMI Scores (%) | SD | Median (%) | Weighted Mean (%) | No. of Studies | Range of Negative PMI Scores (%) | SD | Median (%) | Weighted Mean (%) |
| Year | | | | | | | | | | |
| 1994 to 2000 | 12 | 27-79 | 18.5 | 46.5 | 46.6 | | | | | |
| 2001 to 2007 | 14 | 8-82 | 26.3 | 60.0 | 41.5 | | | | | |
| 2008 to 2013 | | | | | | 20 | 4-68 | 19.9 | 37.1 | 31.8 |
| Geographic area | | | | | | | | | | |
| North America | 8 | 8-65 | 19.1 | 33.0 | 39.1 | 5 | 25-46 | 9.4 | 34.4 | 32.0 |
| Europe | 8 | 9-82 | 26.6 | 51.0 | 40.3 | 8 | 4-63 | 22.7 | 25.7 | 29.5 |
| Asia | 9 | 27-79 | 17.5 | 69.0 | 59.1 | 5 | 12-68 | 21.7 | 41.7 | 45.2 |
| Australia | — | — | — | — | — | 1 | — | — | 20.2 | 20.2 |
| Africa | 1 | — | — | 31.0 | 31.0 | 1 | — | — | 63.1 | 63.1 |
| Economic level | | | | | | | | | | |
| Low to medium | 4 | 31-79 | 21.0 | 68.0 | 52.6 | 4 | 40-68 | 12.4 | 61.6 | 58.6 |
| High | 5 | 41-75 | 15.3 | 74.0 | 58.7 | 3 | 4-15 | 5.6 | 12.0 | 13.1 |
| Very high | 17 | 8-82 | 22.3 | 42.0 | 38.9 | 13 | 10-63 | 15.7 | 34.4 | 32.5 |
| Setting | | | | | | | | | | |
| Specific for cancer pain | 15 | 8-79 | 21.3 | 53.5 | 52.2 | 8 | 4-60 | 16.8 | 37.1 | 28.7 |
| Nonspecific | 5 | 29-74 | 23.4 | 46.5 | 42.8 | 8 | 10-68 | 24.3 | 51.5 | 40.7 |
| Mixed | 5 | 9-82 | 27.0 | 58.0 | 44.6 | 4 | 15-42 | 11.7 | 22.7 | 28.7 |
| Stage of disease | | | | | | | | | | |
| ≥ 68.8% metastatic | 8 | 13-65 | 16.5 | 39.5 | 31.2 | 4 | 4-26 | 9.2 | 12.4 | 19.3 |
| < 68.8% metastatic | 12 | 29-82 | 17.7 | 66.0 | 58.4 | 3 | 25-62 | 18.4 | 41.0 | 37.8 |
| Class age, years | | | | | | | | | | |
| < 58 | 11 | 8-82 | 21.5 | 43.0 | 53.6 | | | | | |
| ≥ 58 | 11 | 27-79 | 19.6 | 65.0 | 55.1 | | | | | |
| ≤ 62 | | | | | | 8 | 12-63 | 16.8 | 40.4 | 40.9 |
| > 62 | | | | | | 9 | 4-68 | 21.8 | 25.3 | 26.5 |
| Male sex, % | | | | | | | | | | |
| ≤ 49 | 12 | 8-79 | 22.8 | 53.5 | 42.9 | | | | | |
| > 49 | 11 | 27-82 | 20.8 | 43.0 | 54.4 | | | | | |
| ≤ 47 | | | | | | 10 | 21-68 | 17.0 | 41.3 | 35.1 |
| > 47 | | | | | | 9 | 4-60 | 18.3 | 25.3 | 28.9 |
| Quality score | | | | 80.0 | | | | | 79.0 | |
| Total | 26 | 8-82 | 22.63 | 51 | 43.4 | 20 | 4-68 | 19 | 37.1 | 31.8 |

Abbreviations: PMI, Pain Management Index; SD, standard deviation.

To test the robustness of results, we also conducted a sensitivity analysis, running the same multivariable model after excluding articles with a quality score was below the 25th and 50th percentiles (67% and 80%, respectively). In these two subsamples of 30 and 19 studies, respectively, the decrease of undertreatment by year was approximately 0.7 ($P = .31$). In the subsample with a quality score above the 25th percentile, nonspecific setting and economic level had a significant relation with PMI score (19.3; $P = .04$ and −0.7; $P = .01$, respectively).

**Table 3.** Change in Undertreatment (negative PMI score) in Relation to Time of Publication

| Year of Publication | No. of Articles | PMI Score Range (%) | Weighted Mean* | Change (%) |
|---|---|---|---|---|
| 1994 to 2000 | 12 | 27-79 | 46.6 | — |
| 2001 to 2007 | 14 | 8-82 | 41.5 | −11 |
| 2008 to 2013 | 20 | 4-68 | 31.8 | −32 |

Abbreviation: PMI, Pain Management Index.
*Percentage of negative PMI scores weighted by sample size for subgroups.

## DISCUSSION

Chronic and acute or episodic pain are frequent and burdensome in patients with cancer.[1,21] To be adequately treated, cancer pain needs to

**Table 4.** Multivariable Analysis of Association Between Collected Variables and Undertreatment (negative PMI scores)

| Variable | Multiple Regression | | | |
|---|---|---|---|---|
| | Estimate | SE | 95% CI | *P* |
| Mixed setting (*v* specific) | 10.76 | 9.29 | −8.30 to 29.82 | .256 |
| Nonspecific setting (*v* specific) | 17.66 | 8.54 | 0.14 to 35.19 | .048 |
| Sample size | 0.01 | 0.01 | −0.02 to 0.01 | .396 |
| Economic level | −0.53 | 0.17 | −0.90 to −0.16 | .006 |
| Age > 62 years | −0.17 | 0.45 | −1.10 to 0.75 | .703 |
| Year of publication | −1.02 | 0.66 | −2.38 to 0.34 | .136 |
| Quality score | 55.63 | 30.21 | −6.35 to 117.62 | .076 |

Abbreviation: PMI, Pain Management Index.

  

be identified, assessed, classified, and managed as part of a multidimensional approach. Pain assessment and classification implies awareness of the existence and importance of the problem and acknowledgment of its intrinsic subjective nature (ie, pain is what patients say it is). Thus, it is always affected by cultural, emotional, spiritual, and behavioral factors related to the host or to the macro- and microenvironments. Valid and reliable tools are also essential; several standardized mono- and multidimensional instruments are currently in use, some even without formal validation. However, there is general agreement on the importance of assessing the intensity of pain, from the patient perspective as well, because this is a basic dimension and a necessary step toward the prescription of an analgesic. Changes in pain over time are also the basis for assessing response to therapy. Therefore, as a fundamental part of pain evaluation, it is best to use a numeric rating scale, referring to the previous 24 hours.[40]

New, more effective therapies and evidence-based guidelines that have become available in recent years provide both the framework and tools to treat cancer pain properly in most cases,[14] but more accurate and better-quality treatments cannot be automatically expected. Reliable estimates based on evidence are needed, particularly from systematic reviews and meta-analyses. In a systematic review published by our group in 2008, we showed that nearly one of two patients was undertreated, with geographic and economic trends in favor of the richest countries. Articles using the PMI as an indicator of analgesic adequacy have suggested a somewhat better performance.[11-13] For example, in an Italian longitudinal cohort study published in 2009, which estimated PMI score on an individual basis, on average, 25% of 1,801 patient cases were undertreated, ranging from 9.8% to 55.3% depending on variables related to patients, centers, and patterns of care.[11] In 2012, in another observational longitudinal study in the United States, Fisch et al[12] reported a 33% rate of negative PMIs, with no differences between baseline and follow-up assessments. In a multicenter study from Canada, Mitera et al[13] reported that approximately 25% of patients with cancer with pain received inadequate analgesic treatment, according to the PMI.

Thus, despite the individual studies reporting improvements in the adequacy of analgesic prescription, our review set out to provide a pooled and more robust analysis of the expected improvement in the quality of analgesic treatments over time. We updated our 2008 systematic review and evaluated new articles published from 2007 to 2013. There seemed to be a progressive improvement in the quality of pain management according to PMI score from 1994 to 2013. The average estimate of patients with a negative PMI score varied from 46.6% during the last years of the 1990s to 31.8% in the most recent period, with a 32% reduction in the percentage of undertreatment, which corresponds to a decrease of 5% every 5 years. This reduction was confirmed by stratified and sensitivity analyses. Among the potential determinants of the undertreatment, only setting of care and economic level showed a significant association with PMI score.

The literature supports this association. China,[29] the Russian Federation,[26] and Nigeria[34] accounted for more than 60% of the negative PMI scores; morphine consumption in these countries[41] during 2011 was 0.7421, 0.377, and 0.0032, placing them 79th, 98th, and 152th in worldwide global opioid consumption ranking, respectively. These countries are also classified as having a medium or low economic level based on IHDIs, despite rapid development. This seems to indicate some causal relation between socioeconomic status, low morphine consumption, and high degree of undertreatment of cancer pain. Appropriateness is necessary to obtain a good outcome; however, response to opioids depends on many other factors, such as a patient's compliance, comorbidities, cotreatments, and genetic profile; the opioid chosen[42]; and the pathogenic mechanisms of pain, among others.

Our study has some limitations related to both the intrinsic characteristics of the PMI and the retrospective nature of this secondary analysis. As previously pointed out,[10,20] the PMI has some limitations to its validity as a tool for measuring the quality of pain management. Pharmacologic appropriateness (ie, congruence between pain intensity and analgesic therapy) is a necessary but not sufficient condition to guarantee good pain control, because analgesic response depends on so many determinants, including pathogenic factors of pain and genetic profiles.[3] The PMI takes into account only two characteristics of analgesic therapy: pain intensity and the most potent opioid prescribed. Other important variables related to the individual patient, pain characteristics, and complementary therapy, such as route of administration, rescue and adjuvant drugs, and use of nonpharmacologic therapies, are not considered. In addition, the analgesic drug prescribed, not its actual administration, is taken into account.

Retrospective analysis of published articles using aggregate data might have had an impact on study precision, because we collected and analyzed the outcome and predictive variables of pain management at the study rather than individual level, which means some loss of sensitivity. In addition, the wide variability of undertreatment prevalence across studies and settings may also be related to some hidden (not measured) variables that were not assessed by the original authors or not reported in the articles and thus not included in our model.

In conclusion, in the new set of 20 articles published from 2007 to 2013, there was a decrease in undertreatment of approximately 25% (from 43.4% to 31.8%). Analysis of the whole sample of 46 studies from 1994 to 2013 confirmed a relationship between time of publication and proportion of undertreatment, suggesting that the quality of pharmacologic cancer pain management has improved; however, approximately one in three patients still does not receive an analgesic prescription to match the reported level of pain.

The increased recognition of the high prevalence and important burden of pain and the documentation of a large proportion of patients receiving inadequate analgesic treatment should reinforce the recommendation that patients with advanced or metastatic cancer need to be treated as part of a more comprehensive strategy for palliative care. This should be targeted to patients and families to increase the ability to identify, assess, classify, and treat cancer pain. Recent evidence suggests that early palliative intervention integrated with anticancer and supportive care can improve the quality of life of patients with lung cancer, reduce anxiety and depression, limit the aggressiveness of care, and extend survival.[43] As pointed out by the American Society of Clinical Oncology,[44] because no trials to date have demonstrated that early palliative care can harm patients or caregivers or induce excessive costs or limit the efficacy of anticancer therapies, combined standard oncology and concurrent palliative care should be considered early in the course of disease for all types of cancer. This approach is a cornerstone when referring to pain management, where accuracy and efficacy of treatments are both crucial.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article.*

*Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*
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**Conception and design:** Maria Teresa Greco, Anna Roberto, Oscar Corli, Silvia Deandrea, Giovanni Apolone
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## *Appendix*

The Pain Management Index described by Cleeland[9] is constructed upon the patient's level of worst pain on the Brief Pain Inventory, categorized as 0 (no pain), 1 (1 to 3, mild pain), 2 (4 to 7, moderate pain), or 3 (8 to 10, severe pain). Then, the pain level is subtracted from the most potent level of analgesic drug therapies as prescribed by the physician, scored as 0 (no analgesic drug), 1 (nonopioid), 2 (weak opioid), or 3 (strong opioid). The index can range from −3 (patient with severe pain receiving no analgesic drug) to +3 (patient receiving strong opioid and reporting no pain). Negative scores indicate inadequate orders for analgesic drugs, and scores ≥ 0 are considered indicators of acceptable treatment.

**Table A1.** Quality Criteria for Studies

| Criterion | Points |
|---|---|
| Final sample should be representative of target population | At least one of following should apply for study: entire target population, randomly selected sample, or sample stated to represent target population (2 points) |
| | At least one of following: reasons for nonresponse described or nonresponders (2 points) |
| | Response rate > 90% (2 points), 70% to 90% (1 point), or < 70% (0 points) |
| Quality of data | Were data primarily from prevalence study (2 points), or were they taken from survey not specifically designed for that purpose (1 point)? |
| | Same mode of data collection should be used for all participants (2 points) |
| | Scale applied to measure pain is reported (2 points) |
| | All cutoffs to define intensity of pain are indicated (2 points); cutoffs only for two levels of pain intensity (1 point); no cutoffs described (0 points) |
| General description of sample size | Descriptions of target population and setting where patients were found (2 points) |
| | Description of stage of disease, type of cancer, sex, age: all (2 points), two or three items (1 point), or not all (0 points) |
| | Final sample size (1 point) |

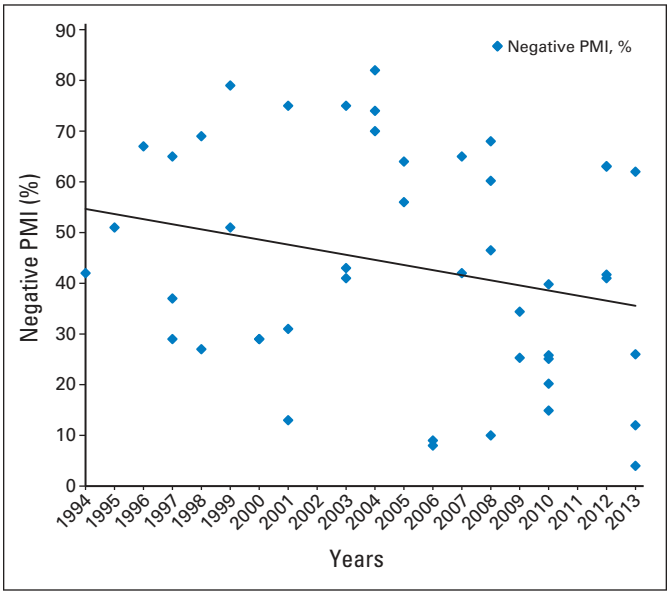


**Fig A1.** Distribution of undertreatment (Pain Management Index [PMI] negative scores) in relation to time (year) of publication.

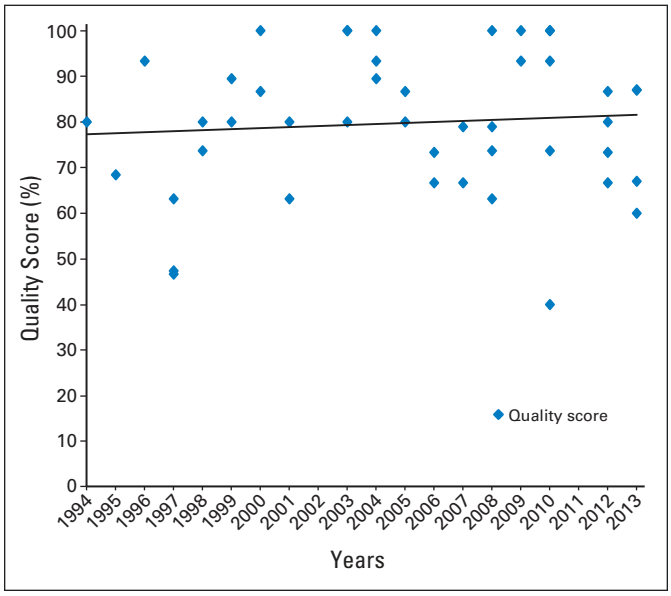


**Fig A2.** Distribution of quality scores in relation to time (year) of publication.