review

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Prevalence of undertreatment in cancer pain. A review of published literature

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Background: Pain is a major health care problem for patients with cancer: despite the existence of guidelines for cancer pain management, undertreatment is a widespread problem. Pain Management Indexes (PMIs) evaluate the congruence between the patient's reported level of pain and the intensity/strength of the analgesic therapy. Negative scores indicate inadequate prescriptions.

Materials and methods: We conducted a Medline search using terms for 'pain management', 'index' or 'measure' to select studies which measured undertreatment in cancer settings. Univariate and multivariate logistic regression identified associations between independent predictors and high prevalence of undertreatment.

Results: Among the 44 studies identified, 26 studies used the PMI as proposed by Cleeland. The range of negative PMI varied from 8% to 82% with a weighted mean value of 43%. In multivariate analyses, factors associated with negative PMI were date of publication before 2001, provenance from Europe or Asia and countries with a gross national income per capita <$40 000 per year and a care setting not specific for cancer. Age was not a significant predictor for undertreatment.

Conclusion: Nearly one of two patients with cancer pain is undertreated. The percentage is high, but consists of a large variability of undertreatment across studies and settings.

Key words: cancer pain, palliative care, quality of care

introduction

Pain is a major health care problem for patients with cancer [1]: a recent meta-analysis reports that 64% of patients with advanced stage disease or metastatic cancer will experience pain [2]. Despite the diffusion of several guidelines for cancer pain management, including well-known recommendations of the World Health Organization (WHO) [3], the Agency for Health Care Policy and Research (AHCPR) [4] and the Expert Working Group of the European Association for the Palliative Care [5] and even if effective treatments are available for 70%–90% of cases [6], undertreatment is well documented and can involve up to 40% of patients [7]. Undertreatment is usually attributed to an inappropriate use of opioids for reasons often conceptualized in terms of barriers related to health care provider, patient, family, institution and society [8].

Several instruments have been created to investigate the presence and grade of undertreatment [9–13]. The Pain Management Index (PMI) is a well-validated method of assessing the adequacy of pain control based on WHO and AHCPR guidelines which was developed by Cleeland et al. [9] for cancer patients in 1994. Pain management is considered adequate if there is congruence between the patient's reported level of pain and the appropriateness of the analgesic therapy. Operationally, patient's worst pain intensity is related to the pain medication as prescribed by the physician. Ward's [10] and Zelman's [11] PMIs use Cleeland's structure with slights modifications: in Ward's version, the worst pain intensity is related to the pain medication as used by the patient; Zelman's version compares current, worst and average pain intensity to the medication used [12]. Some authors have subsequently modified Cleeland's index to improve its validity and sensitivity: Ward et al. [13] proposed a more complex index (PMI-Revised) in order to take into account the patient's least pain scores as well. De Wit et al. [12] proposed a further revision (Amsterdam PMI) in order to incorporate other dimensions of pain experience: current and average pain intensity, individual threshold of tolerability of pain, noncompliance to the therapy prescribed and the whole pain medication (including all opioids and non opioids) actually taken by the patient.

The objectives of this work are (i) to identify and describe all the studies conducted between 1987 and 2007 which assessed

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pain undertreatment using PMIs; (ii) to estimate the prevalence of undertreatment in an homogeneous sample of cancer patients using the most common index and (iii) to examine whether a priori selected variables (i.e. location, disease stage) could help in better understanding the epidemiology of the phenomenon.

materials and methods

Studies were identified in Medline, by scanning references and through consultation with experts in the field. The search strategy used the following terms: 'pain management' AND (index OR measure). No limits were applied for language. The search only included records from January 1987 through October 2007 because 1987 is the date Zelman et al. [11] first presented data about the use of a PMI in cancer patients. We defined the following eligibility criteria: (i) computation of PMI score for each patient and (ii) reporting of the percentage of negative PMI in the study sample. Our operational definition of PMI was 'an index that subtracts the patient's rating of pain from the rating of the strongest analgesic agent'. The eligibility assessment was carried out by a standardized manner by one reviewer (SD). Details of study design, participants, disease, setting, outcome assessors, PMI and methods to compute were recorded. Information was extracted using a pro forma process piloted on a random sample of papers. In order to select the most used index, the different PMIs were ranked on the basis of the number of studies that used them.

Finally, from the studies retrieved, we further selected only those which: (i) computed PMI according to the most used index and (ii) investigated pain in cancer patients, regardless of the care setting (i.e. cancer care ward versus general medical ward).

Among the included papers, we also collected possible determinants of a negative PMI that were referred by the authors of individual studies as a possible predictor of a high prevalence of negative PMI.

We reported the frequency of the different determinants of each article. Whenever there was sufficient variability, we analyzed that characteristic by the direction of results to assess whether certain determinants were associated with negative PMI. Moreover, some other epidemiological factors have been hypothesized to be independently related to negative PMI, mostly for economic, political and social reasons, such as differences between high- and low-resource settings. All these potential predictors of a high prevalence of negative PMI were investigated across studies. The predictor variables considered were as follows:

- Year of publication as a proxy of year of study conduction because several papers did not report this information. The papers were divided between those published before 2001 (median year) and those published in 2001 or after.
- Geographic area: this was split into Asia, Europe and North America. Israel was included in Asia because of its continental location. South Africa was the source of a single study, and it could not have been assimilated to the other geographical categories.
- Economic level: we used the gross national income (GNI per capita) converted in US dollars following the World Bank Atlas method divided by the midyear population as a proxy of the country development level. Data were extracted from the World Bank Data and Statistics [14]; they were updated to 2006 for each country except for Israel, where data are relative to 2005. Papers were classified into those coming from a country with a GNI pro capita <$20 000, with a GNI between $20 000 and $40 000 and with a GNI ≥$40 000.
- Setting in which the patients enrolled in the study were treated: this was classified as specific for cancer patients (i.e. oncology hospitals and wards, hospices), not specific (i.e. general wards, general practice) and mixed.
- Stage of the disease: this was estimated by classifying the papers according to the percentage of patients in the sample with metastatic or advanced disease, when available, and adopting the mean value (68.8%) as a cut-off.
- Age of patients: this was estimated considering the mean age of the sample for each article (median when the mean age was not provided) and was classified in two levels using the median across papers (57.5 years) as a cut-off.

Finally, the range of negative PMIs, standard deviation, median and mean weighted by sample size for the whole study pool and for subgroups described were computed. Multivariable logistic regression analysis was used to describe the relationship between the response variable (each study was classified into one of two mutually exclusive levels according to the level of undertreatment: 0 if PMI ≥51% and 1 if PMI <51%) and a list of potential explanatory variables (year of publication, geographical area, economic level and setting of care). All selected variables were weighted for study sample size and for this analysis geographical area and economic level were dichotomized into non-USA versus USA and <$40 000 versus ≥$40 000 to evaluate the association with respect to the best category found at the descriptive step. Each variable was controlled for all the others included in the model.

results

The search of Medline produced 1115 citations; on a first sift, 453 citations were immediately discharged being irrelevant for that issue; review of the titles and abstracts of the remaining 662 papers, integrated by scanning the references and consulting the experts in the field, yielded 46 relevant articles [9–13, 15, 16, 18–41, Appendix]. An area of concern was the amount of multiple publications for the Amsterdam PMI. The comparison of different PMIs in the same patient group (313 Dutch cancer patients) was published more than once [12, 15, 16]. We selected the first publication computing PMI for that sample of patients [15]. The main characteristics of the 44 original studies are reported in Table 1. The majority of them (79.6%) chose to define PMI as proposed by Cleeland et al. [9]; seven studies (15.9%) computed Ward's PMI [10] and two studies used Zelman's PMI [11] (4.6%). Three studies (6.8%) computed more than one index in order to compare different measures of pain management. A brief description of most used indexes is presented in Box 1. The disease most frequently selected was cancer (75%), followed by AIDS (11.4%).

Our final sample of 26 papers consisted of those that used the PMI Cleeland in cancer patients [9, 15, 18–41]. A brief description of studies included is reported in Table 2. Some studies used PMI computation methods slightly different from Cleeland's original proposal [9], such as an alternative categorization of pain level. These studies followed a different classification of the pain experience proposed by Serlin in 1995 [17], in which pain scores of 1–4 correspond to mild pain, scores of 5–6 to moderate pain and scores of 7 or greater to severe pain.

In 14 studies, the authors of the original papers tried to recognize prognostic factors for undertreatment. The variables most commonly considered are described in Table 3: sociodemographic status (age, gender, race, education) [9, 15, 18–20, 24, 27, 32, 34–36], disease stage (presence of distant

Table 1. Main characteristics of 44 original studies in terms of type of PMI computed and patients' disease

	No. of studies (%)
Type of PMI computed[a]	
PMI Cleeland[b]	35 (79.6)
PMI Ward[c]	7 (15.9)
PMI Zelman[d]	2 (4.6)
Disease[e]	
Cancer patients	33 (75.0)
AIDS patients	5 (11.4)
Other	7 (15.9)

[a]Some studies present more than one PMI type. In two studies it was not possible to detect the type of PMI computed.
[b]Computed as analgesic prescribed − worst pain intensity.
[c]Computed as analgesic actually used − worst pain intensity.
[d]Computed as: analgesic actually used − [present pain intensity + average pain intensity + worst pain intensity]/3.
[e]Some studies consider more than one category of patients' disease.
PMI, Pain Management Index.

Box 1: Pain Management Indexes

Cleeland's PMI is constructed upon the patient's level of worst pain on the Brief Pain Inventory categorized as 0 (no pain), 1 (1–3, mild pain), 2 (4–7, moderate pain), or 3 (8–10, 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 (a weak opioid) or 3 (a strong opioid). The index can range from −3 (a patient with severe pain receiving no analgesic drug) to +3 (a patient receiving strong opioids and reporting no pain). Negative scores indicate inadequate orders for analgesic drugs, and score of 0 and higher are considered indicators of acceptable treatment.

Zelman's PMI measures pain intensity as the mean among present pain, average pain and worst pain.

Ward's PMI considers the analgesic therapy actually used by the patient instead of the physician's prescription.

metastasis, performance status) [9, 18–20, 24, 27, 32, 34–36] and pain characteristics (intensity, discrepancy between physician's and patient's rating of pain severity) [9, 18, 20, 24, 32, 33, 35]. The results regarding the predictive role of age are not consistent: five studies [19, 24, 27, 32, 36] found no relation, three studies [9, 34, 35] reported that older patients are treated worse than younger ones, but another study [18] reported a significant favorable role played by advanced age. Only two studies [15, 24] of 10 reported that being female is an indicator of worse pain treatment. Patients who were rated less ill (better PS) and at an early stage of the disease (no distant metastasis) in more than half of the 10 studies which considered these aspects were more likely to receive inadequate analgesia. One [9] of two studies found that minority or less-educated patients are more likely to be undertreated. The discrepancy between the physician's and patient's estimate of the severity of pain is an undertreatment predictor consistently detected across studies (four of five).

Table 4 reports the range of negative PMIs, standard deviation, median and mean weighted by sample size for the whole study pool and for selected subgroups. The range of negative PMIs varied from 8% to 82% with a weighted mean value of 43%. The high values of standard deviations and pain ranges indicate a high variability within and across subgroups.

After adjusting for the confounding effect of potential covariates, year of publication, country (in terms of geographical location and economic level) and setting showed to be associated with the probability of a higher proportion of PMI negative values. Socioeconomical variables appears to be the strongest determinant for undertreatment, with a multivariate odds ratio (OR) for European and Asian countries of 7.26 [95% confidence interval (CI) 5.75–9.15] versus United States and a multivariate OR for countries with GNI <$40 000 of 5.84 (95% CI 5.03–6.79) versus countries with GNI ≥$40 000 (Table 5). The multivariate OR for papers published before 2001 versus papers published in 2001 or after was 4.73 (95% CI 3.94–5.67).

discussion

Our analysis of 26 relevant studies showed that 43% of cancer patients have a negative PMI score: nearly one of two patients is undertreated. Such a percentage is exceedingly high, but a temporal trend suggests a slight improvement in cancer pain management throughout the years. It is likely that this condition comes from a situation in progress due to better medical education and greater attention paid by national and international agencies such as WHO [42] and The Joint Commission [43]. A geographical and economical trend emerged as well in favor of the United States and other rich countries. Wealthier health systems can sustain and encourage a better pain management through pain control campaigns and drug full covering by national health systems or health insurances. The multivariate analyses also showed an association between negative PMI and settings not specific for cancer patients, maybe due to a lack of specific education in pain management for physicians who have not specialized in oncology or palliative care.

Once the percentage of undertreated patients using a pain index was determined, several investigators tried to identify prognostic factors. Gender and advanced age do not seem to play a role consistently. Patients who were rated less ill (better Performance Status) and at an early stage of the disease (no distant metastasis) were more likely to receive inadequate analgesia. A possible explanation is that patients who look less ill may also be judged to have less pain [9, 44]. A different interpretation of this result is that metastatic patients are treated by a pain expert more frequently than patients at an earlier stage of disease. The discrepancy between the physician's and patient's estimate of the severity of pain experienced and the potential role played by education and ethnicity can suggest that a failure in physician–patient communication may also play a role in undertreatment genesis.

Although PMI is not accurate for prescribing drugs for an individual and not appropriate to evaluate quality of care at an

Table 2. Description of 26 original studies that report PMI Cleeland in cancer patients according to the year of publication, the country where the investigation was conducted, the sample size and the percentage of negative PMI

Name of the first author (reference)	Year (publication)	Country	No. of patients	Percentage of negative PMI (95% confidence interval)[a]	Notes
Cleeland [9]	1994	United States	597	42 (38–46)	
Larue [18]	1995	France	270	51 (45–57)	
Wang [19]	1996	China	147	67 (59–75)	
Cleeland [20]	1997	United States	197	65 (58–72)	Minority outpatients with recurrent or metastatic cancer
Elliott [21]	1997	United States	314	16[b], 41[b]	16% for patients reporting pain in the 3 months before the interview, 41% for patients reporting pain at the time of the interview
Trowbridge [22]	1997	United States	320	38 (31–46), 35 (28–42)	38% in control group, 35% in intervention group
Ger [23]	1998	Taiwan	113	69 (61–78)	
Uki [24]	1998	Japan	121	27 (19–35)	
Saxena [25]	1999	India	200	79 (73–85)	
de Wit [15]	1999	The Netherlands	313	49 (43–55)	Compares the three PMIs: PMI Cleeland (48.9%), PMI Ward (55.1%), PMI Zelman (35.9%)
Anderson [26]	2000	United States	108	31 (17–45); 28 (17–39)	31% for African-American patients, 28% for Hispanic patients
Wells [27]	2000	United States	139	29 (22–37)	
Mystakidou [28]	2001	Greece	220	76 (70–82)	
Sabatowski [29]	2001	Germany	905	13 (11–15)	
Beck [30]	2001	South Africa	426	31 (27–35)	
Cascinu [31]	2003	Italy	117	43 (34–52)	Uses a present pain intensity scale
Shvartzman [32]	2003	Israel	218	75 (69–81)	
Hyun [33]	2003	Korea	508	41 (37–45)	
Yun [34]	2004	Korea	132	74 (67–82)	Computes PMI-Revised as well
Di Maio [35]	2004	Italy	752	82 (79–85)	Non-small-cell lung cancer patients. Uses the quality of life questionnaires
Okuyama [36]	2004	Japan	138	70 (62–78)	
Cohen [37]	2005	Israel	39	56 (40–72)	
Lin [38]	2005	United States	102	64 (55–73)	Prison inmates
Passik [39]	2006	United States	100	8 (3–13)	Considers also 73 AIDS patients (33% has a negative score)
Russell [40]	2006	UK	864	7 (3–11), 9 (7–11)	7% for hospice patients, 9% for patients treated by general practitioners. Uses the Palliative Outcome Scale
Enting [41]	2007	The Netherlands	244	65 (59–71)	

[a]Computed on the basis of the data reported in the paper.
[b]It is not possible to compute 95% confidence interval because of some missing data.
PMI, Pain Management Index.

individual level, it provides a rough estimate of how pain is treated in the population. However, it does not take into account other aspects of the complex problem of cancer pain management: the patient's compliance to the therapy [10], the dosage [45] and route of administration of the most potent analgesic prescribed, potential associations with further analgesic adjuvant drugs (i.e. antidepressants, anticonvulsants) and with other nonpharmacological therapies (i.e. acupuncture, biofeedback). Also, the index takes into account drugs recently prescribed but not yet taken, thus patients with severe pain who were prescribed morphine at the time of the survey are classified as adequately treated. Some authors developed alternative indexes [10–13] just to incorporate in the score some of these additional aspects. When the PMI Cleeland, Ward and Zelman were compared by de Wit et al. [15], the percentage of agreement was very high, especially for Cleeland and Ward (kappa from 0.81 to 1.00), which suggests a broad overlap and a common structure among these measures. The Amsterdam PMI, on the contrary, showed only a fair agreement with the three PMIs [12], meaning that it may give an estimate of pain treatment adequacy different from the other three. Once these limitations

are considered, PMI Cleeland can be used not to obtain a score of any aspect related to pain management, but to find out the consistency between the physician's order and good practice guidelines. The usefulness of this indicator is proved by the great number of studies that have used this score since 1994, and its application to medical conditions other than cancer, particularly for AIDS.

Our study recognizes some limitations: some shortcomings are related to the intrinsic characteristics of the instrument used, whereas others are related to the impossibility of excluding the existence of additional studies which used PMI that were not published or not retrievable through Medline with the search method used. Also, the attempt of identifying variables predictive of better pain management, carried out on a study level and not on an individual patient level, carries significant risk of low sensitivity.

In addition, the large variability of undertreatment prevalence across studies and settings maybe also related to some hidden (not measured) variables that could not be taken into account in our univariate and multivariate analyses because they were not assessed by original authors and thus not reported in the papers. This fact is suggested by the results from an ongoing prospective study carried out in Italy in 2007 [46, 47] where PMI Cleeland was prospectively utilized to assess the prevalence of undertreatment in a cohort of 1801 cancer patients seeking care in 110 Italian oncologic and palliative centers. Overall, the prevalence of PMI negative scores at the time of study inclusion was ~25%, with large variations according to several variables including patients, centers and settings characteristics, such as presence of bone metastasis, ongoing chemotherapy or adjuvant therapy and type of recruiting centers (oncologic or palliative). The case-mix of the cases recruited yielded a large variability across subgroups, reaching a prevalence of up to 45% in some subgroups.

In conclusion, PMI maybe useful in evaluating the quality of the analgesic care in large sample cases. The proportion of

Table 3. Variables affecting PMI frequently investigated in studies included

Variable	No. of papers that study this variable	No. of papers that find this variable affecting PMI
Advanced age	9	4
Female gender	10	2
Race	2	1
Education	2	1
Performance status	9	4
Stage of the disease and/or presence of metastasis	5	5
Pain intensity	2	2
Discrepancy between the pain rate given by patient and by the physician	5	4

PMI, Pain Management Index.

Table 4. Range of negative PMI, standard deviation, median and mean weighted by sample size for selected subgroups and for the whole study pool

Characteristics of studies	No. of studies	Range of negative PMI (%)	Standard deviation	Median	Weighted mean
Year					
1994–2000	12	27–79	18.47	46.5	46.6
2001–2007	14	8–82	26.33	60.0	41.5
Geographic area					
United States	8	8–65	19.14	33.0	39.1
Europe	8	9–82	26.62	51.0	40.3
Asia	9	27–79	17.47	69.0	59.1
Economic level					
GNI per capita < $20 000	8	31–79	17.37	68.0	53.7
GNI per capita $20 000–$40 000	7	13–82	25.75	51.0	48.2
GNI per capita ≥$40 000	11	8–65	20.72	37.0	34.2
Setting[a]					
Specific for cancer patients or hospice[b]	15	8–79	21.33	53.5	52.2
Not specific[b]	5	29–74	23.45	46.5	42.8
Mixed	5	9–82	27.00	58.0	44.6
Stage of disease[a]					
At least 68.8% metastatic	8	13–65	16.54	39.5	31.2
<68.8% metastatic	12	29–82	17.75	66.0	58.4
Mean age of the sample[a]					
≥58 years old	11	27–79	19.62	65.0	55.1
<57 years old	11	8–82	21.52	43.0	53.6
Total	26	8–82	22.63	51	43.40

[a]In some of the studies included in the review this characteristic was not specified.
[b]PMI score extracted from Russel et al. has been splitted.
PMI, Pain Management Index.

Table 5. Univariate and multivariate ORs and 95% CIs of negative PMI ≥51% according to selected variables

Characteristic	Category	Negative PMI ≥median (51%)		
		Studies	Univariate	Multivariate
		n/total *n* (%)	OR (95% CI)	OR (95% CI)
Year	1994–2000	6/12 (50)	1.33 (0.28–6.28)	4.73 (3.94–5.67)*
	2001–2006	8/14 (57)	1	1
Geographic area	United States	2/8 (25)	1	1
	Europe	5/8 (63)	5.00 (0.58–42.80)	7.26 (5.75–9.15)*
	Asia	7/9 (78)	10.50 (1.11–98.91)	
Economic level	GNI per capita <$20 000	6/8 (75)	5.25 (0.70–39.48)	5.84 (5.03–6.79)*
	GNI per capita $20 000 - $40,000	4/7 (57)	2.33 (0.34–16.18)	
	GNI per capita ≥$40 000	4/11 (36)	1	1
Setting	Specific for cancer patients or hospice[a]	8/15 (53)	1	1
	Not specific[a]	2/5 (40)	0.75 (0.08–6.96)	2.11 (1.68–2.65)*
	Mixed	4/5 (80)	1.50 (0.20–11.09)	2.21 (1.92–2.55)*
Stage of disease	At least 68.8% metastatic	2/8 (25)	1	Not included in the model
	<68.8% metastatic	9/12 (75)	9.00 (1.14–71.04)	
Mean age of the sample	≥58 years old	5/11 (45)	1	Not included in the model
	<57 years old	8/11 (73)	3.20 (0.54–18.98)	

[a]PMI score extracted from Russel et al. has been splitted.
*$P < 0.0001$.
OR, odds ratio; CI, confidence interval; PMI, Pain Management Index.

cancer patients whose pain is undertreated is still high, reaching almost a half of all the patients considered in this review. Variability of its occurrence in this sample of studies suggests important pain determinants: geographical area (Europe and Asia), countries with lower economic level and setting not specific for cancer care and management. These results are important for implementing policies to reduce inappropriate high pain prevalence and to address barriers to pain control in the neglected context.

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appendix

Original studies not included in the final sample (disease other than cancer, PMI used not clear or different from Cleeland's) and not cited in the article which computed PMI score for each patient and reported the percentage of negative PMI.

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