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REVIEW

Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review

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Abstract: Inadequate cancer pain relief has been documented extensively across historical records. In response, in 1986, the World Health Organization (WHO) developed guidelines for cancer pain treatment. The purpose of this paper is to disseminate the results of a comprehensive, integrative review of studies that evaluate the effectiveness of the WHO guidelines. Studies were included if they: 1) identified patients treated with the guidelines, 2) evaluated self-reported pain, 3) identified instruments used, 4) provided data documenting pain relief, and 5) were written in English. Studies were coded for duration of treatment, definition of pain relief, instruments used, findings related to pain intensity or relief, and whether measures were used other than the WHO analgesic ladder. Twenty-five studies published since 1987 met the inclusion criteria. Evidence indicates 20%–100% of patients with cancer pain can be provided pain relief with the use of the WHO guidelines – while considering their status of treatment or end-of-life care. Due to multiple limitations in included studies, analysis was limited to descriptions. Future research to examine the effectiveness of the WHO guidelines needs to consider recommendations to facilitate study comparisons by standardizing outcome measures. Recent studies have reported that patients with cancer experience pain at moderate or greater levels. The WHO guidelines reflect the knowledge and effectual methods to relieve most cancer pain, but the guidelines are not being adequately employed. Part of the explanation for the lack of adoption of the WHO guidelines is that they may be considered outdated by many because they are not specific to the pharmacological and interventional options used in contemporary pain management practices. The conundrum of updating the WHO guidelines is to encompass the latest pharmacological and interventional innovations while maintaining its original simplicity.

Keywords: cancer, pain, World Health Organization, review, guidelines

Introduction

Cancer is the leading cause of morbidity and mortality worldwide with ~14 million new cases and 8 million cancer-related deaths in 2012.[1] Furthermore, the International Agency for Research on Cancer estimates the number of new cases to rise by ~75% over the next two decades. More than 50% of people diagnosed with cancer will experience physical pain and of those people, more than one-third will experience moderate-to-severe pain levels.[2,3] The estimated increase in the incidence and prevalence of cancer supports the prediction of an increase in the number of people with pain caused by the disease and its treatment.

Historically, the continued prevalence and extreme intensity of cancer pain experienced by patients have been documented via numerous international epidemiologic studies. More than 40 years ago, Marks and Sachar[4] found that 75% of patients

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experienced cancer pain in spite of analgesics ordered by health care providers. Inadequate cancer pain relief was reconfirmed in later studies.[5–8] After recognition of an international problem, the World Health Organization (WHO) responded by the wide distribution of the WHO Cancer Pain Relief guidelines in 1986,[9] herein, referred to as the WHO guidelines, and subsequently updated the guidelines a decade later.[10] The main element of the WHO guidelines established medical management of cancer pain with a three-step ladder (Figure 1). The purpose of the ladder was to make pain relief available readily to patients with cancer with advanced disease by using effective and inexpensive drugs administered regularly, orally, and on an individual basis while also focusing on safety.[11] In addition, the WHO guidelines were to facilitate and legitimize the use of "strong" opioids (ie, morphine and its derivatives) in regions of the world where the use of these medications was unacceptable or illegal.[11,12]

Despite multiple translations and broad distribution of the WHO Cancer Pain Relief guidelines, inadequate pain relief still exists.[13–16] The effectiveness of these guidelines needs to be evaluated to determine the underlying reason for the continuation of inadequate pain management despite medical advances in the past 28 years. The purpose of this paper is to disseminate the results of a comprehensive, integrative review of studies that evaluate the effectiveness of the WHO guidelines. A key consideration in the evaluation of these studies is to differentiate between those individuals for whom the guidelines are effective and those for whom they are not. This distinction will aid in focusing future research and guideline considerations.

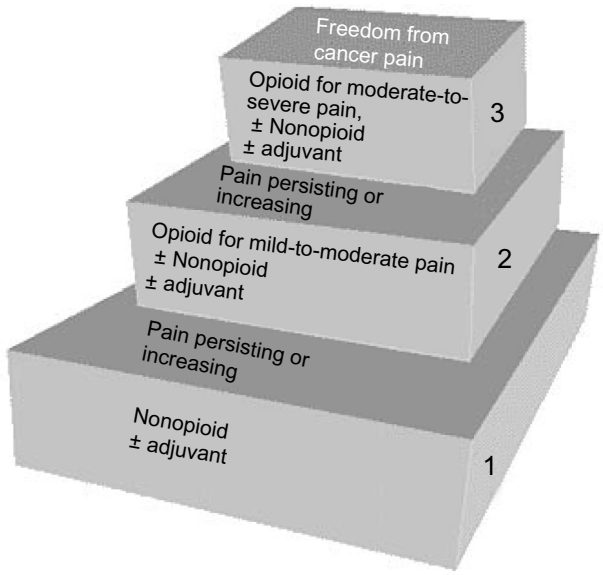

Figure 1 WHO analgesic ladder.
Abbreviation: WHO, World Health Organization.

Two previous reviews of the effectiveness of the WHO guidelines were found in the literature.[17,18] Jadad and Browman[17] identified eight studies for review in 1995 and Ferreira et al[18] identified 17 studies in 2006. Many of the same studies were included in both reviews. There were no randomized clinical trials in the reviews that could provide unbiased estimates of the proportion of patients for whom the WHO guidelines would be efficacious. Indirect measures of effectiveness of pain treatment, however, ranged from 45% to 100% within the two reviews. Multiple limitations were identified across the reviews, including small sample sizes, variable or short follow-up periods, and high exclusion or dropout rates. Jadad and Browman[17] also concluded that there was a lack of homogeneous criteria across studies to assess pain and treatment outcomes to compare effectiveness of the WHO guidelines efficiently and accurately. Ferreira et al[18] discussed that complete relief of pain is rarely achieved in patients with cancer experiencing cancer pain, but pain intensity or duration can be reduced while using the WHO guidelines. Effectiveness of the WHO guidelines was recognized, but the extent and predictability of the effectiveness across studies were being questioned.[17]

This current paper expands what has previously been reviewed evaluating the WHO guidelines. In addition to critiquing previously published work for effectiveness of the guidelines, this review encompasses other pain measurement scales. This review categorizes adequate treatment effectiveness as the pain intensity being 1) less than moderate; 2) a visual analog scale (VAS), numerical rating scale (NRS), and verbal rating scale (VRS) score ≤3 on a 0–10 scale (or 30 on a 0–100 point scale); or 3) a decrease in the pain intensity on the VAS, NRS, or VRS by 70% or more; a decrease in the Integrated Pain Score (IPS) by 70% or more; or an increase in pain relief by 70% or more. The present paper includes studies that were not evaluated by the previous reviews and includes studies that were published in the past decade. The present study included searching more resources than databases and a manual search of reference lists.

Search methods

This review includes health professional literature published within a 28-year period between 1987 and May 2015. The timeline reflects the period that began immediately following release of the first guidelines from the WHO in 1986.

Four methods were used to identify studies for review. A comprehensive computer search was conducted using

Cumulative Index of Nursing and Allied Health Literature (CINAHL), MEDLINE, Proquest, and PubMed. Medical Subject Headings (MeSH) and text words (txt) used in the search included "pain" [MeSH and text] and "cancer" [txt] or "neoplasms" [MeSH] in combination within the full text: "relief" [txt], "control" [txt], "prevalence" [MeSH and txt], "intensity" [txt], "intractable" [txt], "management" [txt], "under-medication" [txt], "palliative care" [MeSH and txt], "analgesia" [MeSH and txt], "analgesic ladder" [txt], "symptom" [txt], "validation studies" [MeSH], and "World Health Organization" [MeSH and txt]. In addition, online indices of individual periodicals were searched using titles and abstracts that were established sources to publish reports of the evaluation of the WHO guidelines. These included *Pain*, *Journal of Pain and Symptom Management*, *Cancer Nursing*, *Pain Management Nursing*, and *Oncology Nursing Forum*. The Internet was searched using multiple search engines such as Google and Google Scholar, Yahoo, Bing, Webcrawler, and Ask.com. Multiple pain-related web pages were searched for abstracts and text related to the evaluation of WHO guidelines including, but not limited to, the WHO, International Association for the Study of Pain (IASP), American Pain Society (APS), American Society of Pain Management Nurses (ASPMN), and the Pain and Policy Studies Group (PPSG). Finally, a comprehensive review of citations within included research studies were also searched for identification of further studies.

Research studies of any methodological design were included in this review if they: 1) specifically identified treatment of adult patients with cancer with the WHO guidelines, 2) evaluated patients' self-reported cancer pain, 3) provided information on the instruments used to measure cancer pain relief, 4) provided data documenting changes in pain intensity via the VAS, NRS, VRS, or IPS after treatment or provided data documenting the proportion of patients experiencing adequate pain control/relief after treatment, and 5) were written in English. Each eligible study available was reviewed and coded for the following information: author(s), publication year, title, source, study design, aims, sample population and size, dates of data collection, country of data collection, duration of treatment, definition of adequate pain relief, instruments used to measure pain, methodology, findings related to pain intensity or relief, and whether additional measures for pain control were used other than the WHO analgesic ladder. The samples of the studies were evaluated for size, randomization, and reasons for termination/exclusion from the study. The quality of the data was evaluated according to the aim(s) of the study, whether data were collected prospectively or retrospectively from the medical record, and the length of the study follow-up periods. The methodology was evaluated by the description of the target population and setting, demographic data of the sample reported, and presence of a control group.

Cooper's guide for integrated literature reviews was used.[19] Quality appraisal was not completed for this review because of a lack of randomized control studies. However, the methodology, bias, and threats to internal and external validity are summarized in the results section. Every study that met the inclusion criteria was included in the analysis.

Results

Forty-eight research studies were identified for review. Several studies shared the same population samples. According to Petitti,[20] failure to exclude studies analyzing the same sample may cause bias in the magnitude of findings. Therefore, only studies using the most inclusive sample were included. For example, there were six studies using the same patient sample in Germany;[21–26] only the latest and most inclusive study is included in the review.[26] In order to ensure accuracy, communication with authors was completed. For example, according to Mercandante, the samples of patients were not the same in studies published in 1992[27] and 1999.[28] Ten studies were removed from review due to overlap of population samples.

Several other studies were excluded as they evaluated the intensity/strength of the analgesic treatment of the patients' reported pain using the pain management index (PMI) developed by Cleeland et al.[29] While the PMI is based on the WHO recommendations for cancer pain relief, the studies using the PMI did not specify whether or not the treatment administered to the patients was based on the WHO guidelines. Without the use of the inclusion criteria language, the relationship to the WHO guidelines was not clear. Thus, 13 additional studies were not included. From the original 48 studies identified, 25 studies fulfilled the inclusion criteria.

In reviewing the 25 included studies, all of the studies used convenience samples, while only four of the convenience samples were randomized. The four studies that used randomized samples were for the purposes of evaluating the necessity of Step 2 of the WHO analgesic ladder[30–32] (Figure 1) or the use of mild opiates.[33] Nineteen of the studies were prospective studies, including six quasiexperimental studies in which four used comparison groups. Only two studies had a control group[32,34] and one study was double-blind.[35] Because of the lack of control groups throughout all but two of the 25 studies, meta-analysis was not performed. Therefore, content analysis of methods and findings is described narratively. Table 1

Table 1 Chronological summary of research studies evaluating the efficacy of WHO Cancer Pain Relief Guideline

Study	Sample size[a] Population	Design	Purpose	Methods Notes	Pain instruments Pain relief definition	Findings
Ventafridda et al[37]	1,229 patients with cancer at the pain division of the National Cancer Institute in Italy from September 1983 to August 1985.	Retrospective, descriptive	To examine how often the WHO analgesic ladder offers pain relief in patients with advanced cancer, how many negative side effects are experienced with this method, and what percentage of patients require neurolytic procedures in addition to the ladder.	Daily duration of pain and pain intensity was assessed via recordings made at home by the patients and with the help of relatives when necessary. Patients were followed weekly until death. Mean duration of treatment was 77 days.	• IPS (0–240 possible but rarely over 100 in this sample) score = hours of duration × intensity by using keywords of slight (1), troublesome (2.5), exhausting (5), terrible (7.5), and excruciating (10) Adequate pain relief was not defined.	Of the 871 patients receiving medications only: • Mean IPS of patients treated with Step 1 went from 54 to 23 after 4 days of treatment (a 57% reduction), Step 2 went from 58 to 30 after 5 days then to 22 over several days (a 62% reduction), and Step 3 went from 64 to 40 in 2 days and then to 20 over several days (a 69% reduction).
Walker et al[38]	20 cancer patients experiencing pain in palliative care unit of hospital in England from February 1985 to July 1986.	Prospective, descriptive	To evaluate the feasibility and efficacy of the WHO guidelines.	Research nurse surveyed patient upon referral for duration of pain, intensity of pain, and pain relief. Patients completed self-assessments daily. Evaluated weekly and recorded by a research nurse until pain control achieved, then evaluated every 4 weeks. Mean duration of treatment was 25 weeks.	• VAS (0–100 mm) • VRS for pain intensity and pain relief Adequate pain relief was not defined.	For the 13 patients treated with medications only during the first week: • Mean VAS decreased from 69 to 36 (a 48% reduction) and daily duration from 12.5 to 6.7 hours • After 18 months, six long-term survivors had a mean pain intensity 61% lower than that on entry with a duration of 4.2 hours.
Goisis et al[40]	45 patients experiencing cancer pain in one internal medicine (not oncology-specific) hospital in Italy from April 1987 to June 1988.	Prospective, descriptive	To verify the efficacy and easy applicability of the WHO guidelines by a personnel not highly specialized.	Patients were assessed at the beginning of therapy and then daily for pain measurement and evaluation of therapy. Mean duration of treatment was 25 days.	• VAS (0–10) Adequate pain relief was defined as complete relief (no pain) or partial relief (an improvement of 75% on VAS).	• Mean VAS decreased from 9.04 to 2.77 (a 69% reduction) after the average period of observation. • Complete relief in 24% and partial relief in 69% rapidly over 3 days and then slowly over subsequent days for a combined total of 93% of patients receiving adequate pain relief.
Takeda[47]	205 patients with cancer pain in a cancer center in Japan from 1983 to 1985.	Prospective, descriptive	To field test the WHO draft interim guidelines.	Patients with cancer were surveyed upon admission for pain location and intensity and at each follow-up (interval not given) for pain and pain relief. Mean duration of treatment was not given.	• VAS • Complete relief = no pain, acceptable relief = >90% relief of pain, partial relief = decrease in severity of pain Adequate pain relief was defined as "complete relief" or "acceptable relief".	• No report on VAS. • 97% reported complete or acceptable pain relief.

Ventafridda et al[34]	110 patients with cancer pain in 25 centers in 15 countries and 261 patients with cancer pain in 6 collaborating centers for implementation of WHO guidelines during 1984–1987.	Prospective, descriptive	To obtain background data on the current practice of pain management in selected centers; to determine the feasibility of using the WHO guidelines in selected clinics; to test the compliance with the WHO guidelines approach; to test the effectiveness of the WHO guidelines in individual patients based on pain reduction with minimal side effects.	Patients with cancer pain from centers without extensive exposure to WHO guidelines were compared to centers knowledgeable about the guidelines. Investigators were to complete a form requesting various data including patient self-assessment form for pain at first visit and a different form at each follow-up visits at the end of the first 2 weeks then at 4-week intervals. If any change in therapy, patient was evaluated again in 2 weeks followed by 4-week intervals until death. Mean duration of treatment was 61 days for patients from non-WHO centers and 34 for WHO centers.	• VRS (four points – none, slight, moderate, severe) • Linear analog pain relief score Adequate pain relief was defined as "none" or "slight" pain.	Percentage of controlled pain (none or slight) was significant between groups after 1 month of treatment: • Control group had 49% of patients reporting controlled pain. • WHO group had 76% controlled pain No report of linear analog pain relief score as it was not understood and correctly used by most centers.
Wenk et al[36]	28 patients with cancer with pain treated until death in their homes from October 1987 to December 1988 through a free pain program in Argentina.	Retrospective, descriptive	To describe the results of the application of a model program for WHO cancer pain relief.	Describes the model used to treat patients with cancer in their homes. Assessed weekly by an anesthesiologist. In the home, patients are assessed 24 hours after the beginning of a treatment and every Monday and Thursday by nonmedical volunteers who had 4–6 months training. Mean duration of treatment was 51 days.	• VRS (not defined) • IPS (not defined) Adequate pain relief not defined.	• VRS not reported. • IPS decreased significantly from 135 to 40 during first days of treatment (a 70% reduction) and then to ~25 (a total of an 81% reduction) for the duration of treatment (data are approximations from graphic representation).
Mercadante et al[27]	98 consecutive opioid-naïve cancer patients with severe or intolerable cancer pain that were followed at home or in an outpatient clinic by an experienced palliative care team	Prospective, descriptive	To establish validity of some factors in predicting the success of pain control using only a pharmacological approach with NSAID and opioids administered per os or parenterally, plus coanalgesics.	Pain assessed 2–3×/w until death. Patients given NSAID, if pain less than moderate within 3 days assigned to group 1. If NSAID not effective, morphine given and if pain less than moderate within 3 days, assigned to group 3. If morphine is not effective within 4 days, assigned to group 5 where dosages were	• VRS (four points: slight, moderate, severe, and intolerable) Adequate pain relief defined as ≤ moderate pain.	Results: number of patients who achieved pain relief at time of death: Group 1: 9/89% Group 2: 7/86% Group 3: 51/86% Group 4: 7/71% Group 5: 8/38% Group 6: 16/25% Groups 1, 3, and 5: 68/81% Groups 2, 4, and 6: 30/50%

(*Continued*)

Table 1 (*Continued*)

Study	Sample size[a] Population	Design	Purpose	Methods Notes	Pain instruments Pain relief definition	Findings
	over 45–75 days until death in Italy. (No data collection dates available.)			escalated. Patients in groups 2, 4, and 6 corresponded with the previous groups but also needed rescue medication. Mean duration of treatment was 58 days.		
Siguan et al[48]	86 patients with pain in one cancer care center in the Philippines from February 1991 to September 1992.	Prospective, descriptive	To evaluate the efficacy and safety of cancer pain treatment using the WHO three-step analgesic ladder.	Patients with cancer evaluated upon admission and at each follow-up. All patients began at Step 1 of WHO analgesic ladder and advanced steps when pain relief score was <50%. Inpatients were evaluated every 24 hours, and outpatients were evaluated every week. Mean duration of treatment was not given.	• VAS (0–10) • PRS of 0%, 25%, 50%, 75%, and 100% Adequate pain relief suggested to be 50%–100% on the pain relief scale.	• 40% were pain free. • 86% had at least 75% pain reduction. • 96% had at least a 50% pain reduction.
Zech et al[26]	2,118 patients with cancer referred to an anesthesiology-based pain service in Germany from 1983 to 1992.	Prospective, descriptive	To test the feasibility and efficacy of the WHO analgesic ladder.	All patients were surveyed upon admission and at intervals according to patient condition for therapeutic treatment and efficacy of treatment. Data collection points were at first follow-up (6 days average), middle of treatment (37 days average), at last follow-up (average 66 days), and at time of death. Mean duration of treatment was 66 days.	• VRS with six points of none, mild, moderate, severe, very severe, and maximal. Pain relief was described as good, satisfactory, and inadequate (severe, very severe, or maximal pain on <10%, 10%–30%, and >30%, respectively, of the patient's treatment period) Adequate pain relief was less than moderate pain.	Pain at first follow-up • Less than moderate: 57% • Moderate or greater: 37% Pain at middle of treatment • Less than moderate: 67% • Moderate or greater: 27% Last follow-up • Less than moderate: 68% • Moderate or greater: 20% Time of death • Less than moderate: 72% • Moderate or greater: 19% Efficacy of treatment: Good: 76% Satisfactory: 12% Inadequate: 12%
Tsui et al[44]	702 patients with cancer experiencing pain who were referred to an anesthesiology department pain management team	Prospective, descriptive	To describe the efficacy of pain treatment.	Assessed every 2 hours for the first 48 hours or until pain relief was adequate and then 3×/d. Fifty seven patients also had blockades. No treatment duration was reported.	• VAS (0–10) Adequate pain relief was ≤3.	Mean pain at baseline: 6.31. Mean pain upon discharge: 1.2 (an 81% reduction). 88% had pain ≤3 upon discharge.

	in one hospital in Hong Kong from January 1992 to March 1996.					
Talmi et al[42]	38 patients with cancer of the head and neck who were experiencing pain admitted for palliative care only at a medical center hospice in Israel. (No data collection dates available.)	Prospective, descriptive	Evaluate the effectiveness of the WHO analgesic ladder in the treatment of a cohort of patients with terminal carcinoma of the head and neck.	Pain assessed upon admission and after treatment for 72 hours and after a second 72 hours if possible.	• VAS (0–10) Adequate pain control/relief was not defined.	VAS scores (mean): • Upon admission: 4.7 (n=48). • Second assessment: 1.9 (n=38) – (a 60% reduction after 72 hours). • Third assessment: 1.6 (n=6) – (a 66% reduction after the 2nd 72 hours).
Minotti et al[35]	180 patients between 18 and 80 with moderate-to-severe pain admitted to a hospital oncology department in Italy between February 1989 and March 1993.	Prospective quasiexperimental, randomized	Evaluate the efficacy and tolerability of diclofenac administered at daily doses of 200 mg in combination with a placebo, a weak opioid, or an antidepressant (imipramine) in patients with chronic cancer pain.	Patients assigned to one of three treatment groups: 1) imipramine plus diclofenac, 2) diclofenac plus codeine, and 3) diclofenac plus placebo. Patients evaluated upon admission and on day 4 (after 3 days of treatment) and day 8 (after 7 days of treatment). If no relief on day 4, patients were withdrawn from the trial and started on another analgesic therapy.	• VAS (0–100) Adequate pain relief was VAS <40 or reduction in VAS of at least 50%.	Mean VAS after 3 days of treatment (n=180): • Group 1: 16.9 • Group 2: 15.8 • Group 3: 23.3 Mean VAS after 7 days of treatment (n=117): • Group 1: 6.9 • Group 2: 7.1 • Group 3: 6.2 Differences between groups were not significant.
Mercadante et al[28]	2,500 patients presented with pain and met the inclusion criteria referred to a home palliative care program in Italy from June 1988 to June 1997.	Prospective, descriptive	Provide information on the effectiveness, safety, feasibility in terms of incidence, and intensity of adverse effects of a pain management program at home on the absis of WHO guidelines.	Patients were referred to home palliative care program because they had metastatic cancer that was no longer responsive to oncologic treatment. Most patients were followed-up until death. Data were collected 2–3 times per week, but data were analyzed upon referral, after 1 week, and in the last week of life. Mean duration of treatment was 64 days.	• VAS (0–10) and classified as mild (1–3), moderate (4–6), and severe (7–10) Adequate pain relief defined as VAS ≤ 3.	VAS score means: • Initial pain intensity: 4.4. • After 3 days of treatment: 3.5 (a 20% reduction). • After 1 week of treatment: 2.5 (a 43% reduction). • Last week of life: 2.3 (a 48% reduction). • 50% had a significant pain (≥ 4) upon referral, 22% after 1 week of treatment, 11% in last week of life.

(*Continued*)

Table 1 (*Continued*)

Study	Sample size[a] Population	Design	Purpose	Methods Notes	Pain instruments Pain relief definition	Findings
Vielvoye-Kerkmeer et al[49]	30 patients referred by oncologists to a pain clinician in one hospital in the Netherlands and suffered from severe chronic cancer pain and needed strong opioids, but were not yet on them. (No data collection dates given.)	Prospective, quasiexperimental	To determine whether transdermal delivery of fentanyl is an adequate treatment for chronic cancer pain in patients for whom codeine (WHO ladder Step 2) or paracetamol/acetaminophen (WHO ladder Step 1) does not provide adequate analgesia any longer.	Treated patients with cancer experiencing escalating pain with transdermal fentanyl with immediate-release morphine as a rescue medication. Fentanyl was given to two groups of patients: 1) opioid-naïve patients (Step 1 on the WHO analgesic ladder) and 2) patients who had used only codeine (Step 2). Thus, Step 2 was skipped in the opioid-naïve patients. Patients were assessed every 3 days when the patch was changed for 4 weeks. Mean duration of treatment not given.	• NRS (0–10) • VRS of treatment efficacy (poor, moderate, good, excellent) Adequate pain relief was "good" or "excellent" efficacy.	• 71% in the opioid-naïve patients and 69% of the codeine using patients rated their pain control as "good" or "excellent". • NRS was represented graphically without specific point labels and without narrative description.
Meuser et al[41]	593 inpatient and outpatient patients with cancer treated by an anesthesiology-based pain service in Germany from August 1992 to July 1994.	Retrospective, descriptive	To investigate the prevalence, severity, and etiology of symptoms during pain therapy for advanced cancer	Patients recorded pain characteristics daily in a pain diary or were assisted to do so. Patients were assessed clinically upon admission to the service and on an average of every 3.2 days by the service. Data for analysis were taken from the admission, first follow-up (average 3.4 days), middle of treatment (average 24.6 days), and last follow-up (51.4 days). In five patients during the first and middle follow-ups, and 16 patients at the last follow-up, nurses or next of kin completed data. Mean duration of treatment was 51.2 days.	• NRS (0–100) • VRS (none, mild, moderate, severe, very severe, maximal) Severe to maximal pain on $<$10% of days was defined as "good", on 10%–30% of days as "satisfactory", and on $>$30% of days as "inadequate".	• Mean NRS for average pain decreased from 66 on admission to 27 (a 59% reduction) at the first follow-up to 21 (a 68% reduction) at the middle follow-up to 18 (a 73% reduction) at the last follow-up. • Mean NRS for maximum pain decreased from 79 to 23 (a 71% reduction) at the last follow-up. • Efficacy of pain relief was good (70%), satisfactory (16%), and inadequate (14%).

Hwang et al[39]	60 patients with cancer experiencing pain referred to hospice home care program in Taiwan from January to December 2000.	Prospective, descriptive	To determine the effectiveness, safety, and feasibility of a pain management based on the WHO method.	Home visits were 2×/w by nurses and 1×/w by physician until death. Data from referral, after 1 week of treatment and in the last week of life were analyzed. Mean duration of treatment was 65 days.	• VAS (0–10) where 1–4 (mild), 5–6 (moderate), and 7–10 (severe) Adequate pain control/relief defined as VAS ≤4.	• VAS decreased from 4.58 upon referral to 2.8 (a 39% reduction) after 1 week of treatment and to 2.02 (a 56% reduction) in last week of life. • 28/60 (47%) patients were experiencing pain >4 upon admission, 9/60 (15%) after 1 week, and 6/60 (10%) patients during the last week of life.
Bostrom et al[62]	75 patients experiencing pain from two hospital-based palliative care teams in Sweden. Of the 75 patients, 47 patients had mild pain (low pain), and 28 patients had moderate-to-severe (high pain). (No data collection dates stated.)	Descriptive, correlational, cross-sectional	To describe and compare pain and HRQoL between patients with cancer with higher levels and lower levels of pain in palliative care.	Compared patients with pain VAS ≤3 and patients with pain >3. Patients assessed 1× by one of two registered nurses. Median duration of treatment was 2 months.	• POM-VAS (0–10) measuring current pain level, worst pain level in 24 hours, average pain level in 24 hours, and pain interrupting sleep Adequate pain control/relief defined as VAS ≤3.	Pain at time of interview: • Low pain group: 1.8 • High pain group: 3.9 Worst pain in past 24 hours: • Low pain group: 3.3 • High pain group: 6.2 Average pain in past 24 hours: • Low pain group: 1.8 • High pain group: 5 Pain interrupting sleep • Low pain group: 1.9 • High pain group: 3.5
Marinangeli et al[33]	92 patients with mild-to-moderate pain with terminal cancer who were provided with home palliative care in Italy. (No data collection dates stated.)	Prospective, quasiexperimental, randomized	To evaluate the use of strong opioids as first-line treatment in patients with terminal cancer and compare this regimen with the recommended WHO guidelines that suggest the use of strong opioids only as third-line treatment.	Compares the use of strong opioids as first-line treatment in patients with terminal cancer (n=44, Group B) with the recommended WHO guidelines using strong opioids as a third-line treatment (n=48, Group A). Patients record pain intensity daily. Patients evaluated weekly until death. Mean duration of treatment was 77 days (Group A) and 79 days (Group B).	• VAS (0–10) Adequate pain control/relief not defined.	Baseline VAS: • WHO protocol: 4.03 • Strong opioids: 4.13 Mean change in pain intensity from baseline over duration of treatment: • WHO protocol: –1.92 (a 48% reduction) • Strong opioids: –2.61 (a 63% reduction)
Mystakidou[72]	1,828 patients in palliative care at WHO Steps 1, 2, and 3 in Greece	Prospective, descriptive, quasiexperimental	Aim of study to examine pain management outcomes and quality of life measures in patients with cancer with intolerable	Patients evaluated at least 1×/d for 3 days after each dose adjustment. Data retrospectively collected from diary cards from	• VAS (0–10) Adequate pain control/relief was defined as VAS ≤2.	• Average pain of groups I, II, and III was reduced from VAS of 7 to VAS of 3 within 7 days (a 57% reduction), VAS of 2 within 14 days (a 71%

(*Continued*)

Table 1 (*Continued*)

Study	Sample size[a] Population	Design	Purpose	Methods Notes	Pain instruments Pain relief definition	Findings
	from May 1996 to April 2002.		or chronic severe pain transferring from WHO I, II, and III analgesics to transdermal therapeutic fentanyl system.	the time points of baseline; 48 hours (minimum data collection point for analysis inclusion); and 7, 14, and 28 days; 2, 4, 6, 8, 10, 18, and 24 months; then 12-month intervals – or until the patient stopped participation in the study because of satisfactory treatment or until death. Mean duration of treatment was 9.2 months.		reduction) where it continued to decline for up to 60 months. • Step 1 (n=286) VAS reduced from 8 to 3 within 7 days (a 63% reduction) where it remained through 14 days. • Step 2 (n=1,239) VAS reduced from 7 to 3 within 7 days (a 57% reduction) where it remained through 14 days. • Step 3 (n=321) VAS reduced from 6 to 2 within 7 days (a 67% reduction) where it remained through14 days.
Maltoni et al[30]	54 patients from multiple cancer care centers in Italy who have pain intensity of 5–6 and are NSAID resistant and whose physicians deemed that opioids are needed (patients were opioid naïve). Data collected over an unknown 24-month period.	Prospective, quasiexperimental, randomized	Verify whether an innovative therapeutic strategy for the treatment of mild-to-moderate chronic cancer pain, passing directly from Step 1 to Step 3 of the WHO analgesic ladder, is more effective than the traditional three-step strategy.	Variables recorded at baseline and up to 90 days. Patients were monitored daily via telephone or weekly at the hospice outpatient clinics. Patients were divided into two groups: Group A was treated with the conventional WHO ladder, and Group B was treated with strong opioids (Step 3 of WHO ladder). Mean duration of treatment was 42 days.	• NRS (0–10) where (0–4 mild, 5–6 moderate, and 7–10 severe) Adequate pain relief was not defined.	• Eliminating Step 2 of the WHO analgesic ladder presented a statistically significant improvement over the traditional three-step analgesic ladder with the percentage of days with worst pain ≥5 (22.8% vs 28.6%, $P<0.001$) and ≥7 (8.6% vs 11.2%, $P=0.023$).
Peng et al[43] (2006)	772 deceased patients with advanced cancer treated at a cancer center in the People's Republic of China from January 2001 to June 2003. Inclusion criteria did not include the presence of pain.	Retrospective, descriptive	Investigate pain management of patients with cancer cared for by oncologists and surgeons – and not by pain clinics.	Chart review of deceased patients for pain presence, its assessment, and treatment. Inpatients were assessed every 6–8 hours; outpatients evaluated every 2 weeks. Data collection points were at 6 months, 3 months, 1 month, 1 week, and 1 day before death.	• NRS (0–10) where pain classifications were mild (1–4), moderate (5–6), and severe (7–10) Adequate pain relief was considered ≤4	• Number of patients with pain increased from 28% at 6 months before death to 79% 1 day before death. Prevalence of pain with a verbal rating of 5–10: • 1%, 6 months prior to death • 3%, 3 months prior to death • 8%, 1 month prior to death • 11%, 1 week prior to death • 6% ,1 day prior to death • Received antineoplastic tx

Keskinbora et al[31]	63 patients with cancer in an anesthesiology pain clinic in Turkey who were receiving opioid therapy and reported adequate relief of nociceptive pain, but not neuropathic pain (NRS ≥4). (No data collection dates given.)	Prospective, quasiexperimental, randomized	Compare the efficacy and safety of gabapentin and an opioid combination, with opioid monotherapy in neuropathic cancer pain management.	Patients randomized into two groups: 1) gabapentin adjuvant therapy titrated according to pain response while opioid dose remained constant and 2) continuation of opioid monotherapy according to the WHO analgesic ladder. Patients were assessed at baseline and every 4 days. Burning and shooting pain were considered features of neuropathic and were used as the discriminate of neuropathic pain from other types. Patient assessments were done on the 1st (baseline), 4th, and 13th days of the study. Duration of the treatment was 13 days.	• NRS (0–10) Adequate pain relief was suggested to be ≤3.	Both groups reported a significant reduction in NRS at day 4 and day 13 compared to baseline. Mean pain intensity for burning and shooting pain was significantly higher in the group treated with opioids only for day 4 and day 13 than for the group treated with opioids and gabapentin. Burning pain: • On day 13, the NRS of the gabapentin group reduced –7.39 from baseline. • On day 13, the NRS of the opioid monotherapy group reduced –5.78 from baseline. Shooting pain: • On day 13, the NRS of the gabapentin group reduced –6.77 from baseline. • On day 13, the NRS of the opioid monotherapy group reduced –4.66 from baseline. All reductions in NRS were represented visually with bar graphs noting statistical differences.
Bhatnagar et al[46]	3,212 patients experiencing cancer pain in an outpatient clinic of a cancer hospital in India over a 5-year period from 1999 to 2004	Retrospective, descriptive	Demonstrate the efficacy of the WHO guidelines in patients experiencing no pain relief with oral pharmacology.	Patients received individualized care through careful patient assessment, consultation with other clinicians in other specialties, and treatment with various methods in which the mainstay was the WHO analgesic ladder. Chart review of recording follow-up findings at 1 week, 1 month, and 6 months.	• VAS (0–10) Adequate pain relief was suggested to be VAS<3.	• 37%, 87%, and 90% of patients had good pain relief at 1 week, 1 month, and 6 months, respectively. • 93% had good pain relief with analgesics.
Subongkot et al[45]	261 patients experiencing cancer pain in one university hospital in Thailand.	Prospective, descriptive, correlational, cross-sectional	Explore the result of cancer pain management.	Patients divided into two groups: opioid naïve and a routine group who were not opioid naïve. Each group subdivided into those who were treated according to WHO pain management guideline and those who were not treated with	• NRS (0–10) Pain classifications were mild (1–3), moderate (4–6), and severe (7–10).	• Naïve group: average pain rating decreased 3.9 points and average of maximum pain was 2.5 on the NRS for those who followed WHO guidelines. Average pain rating decreased 2.2 points and average of maximum pain was 4.4 for those who did not follow the guidelines.

(*Continued*)

Table 1 (*Continued*)

Study	Sample size[a] Population	Design	Purpose	Methods Notes	Pain instruments Pain relief definition	Findings
				the WHO pain management guideline (determination of how these subgroups were divided is unclear except that pain severity, analgesics around the clock, and analgesics for break-through pain were considered) for 3 days after admission.		• Routine group: average pain rating decreased 3.9 points and average of maximum pain was 1.4 on the NRS for those who followed WHO guidelines. Average pain rating decreased 3.1 points and average of maximum pain was 4.0 for those who did not follow the guidelines.
Nunes et al[32]	53 outpatients with locally advanced and/or metastatic disease in one university hospital in Brazil.	Prospective, descriptive, quasiexperimental	To evaluate the use of morphine as first medication for the treatment of moderate cancer pain with advanced/metastatic disease.	Patients randomly divided into two groups with the first group following Step 1 of WHO guidelines and progressing through the steps as warranted and the second group starting with Step 3 who were initiated with morphine. Patients monitored for 12 weeks with pain evaluated every 2 weeks.	• VAS (0–10)	• Pain steadily decreased for both groups over the 12 weeks with no statistical difference between groups. • 60% decrease in pain intensity for the group following the WHO guidelines from Step 1. • 50% decrease in pain intensity for the group initiated on Step 3 with morphine.

Note: [a]Number of patients who were treated with the ladder and from whom data were available.

Abbreviations: WHO, World Health Organization; IPS, Integrated Pain Score; VAS, visual analog scale; VRS, verbal rating scale; NSAID, nonsteroidal anti-inflammatory drugs; PRS, pain reduction scale; NRS, numerical rating scale; POM, Pain-O-Meter; HRQoL, health-related quality of life.

chronologically summarizes the individual research studies that measure the effectiveness of the WHO guidelines.

Findings from the longitudinal studies were classified into five categories: 1) the percentage of patient responses that demonstrated a reduction in the IPS, 2) the percentage of patient responses for whom the reduction in the VAS or NRS was stated or could be calculated, 3) the percentage of patient responses that were within the categories created from scores on the VAS or NRS that was considered as controlled pain or adequate pain relief, 4) the percentage of patient responses on the VRS of pain relief or the VRS of pain intensity that were considered as adequate pain relief, and 5) others that did not classify findings into the previous four categories.

Two studies used the IPS.[36,37] The IPS was designed to take into account both pain intensity and duration when assessing patients' pain. It is calculated by multiplying the hours of pain duration per day by the pain intensity using a 10-point VAS, NRS, or points assigned to a VRS. Thus, scoring of the IPS has a range of 0–240 possible points. In the first few days of treatment with the WHO guidelines, Wenk et al[36] found patients experienced a 70% reduction in the IPS,[36] while Ventafridda et al[34] found patients experienced a 57% reduction.[34] Progressive treatment led to an 81%–69% reduction in pain scores, respectively. Overall, the reduction in the IPS after initiation of treatment ranged from 57% to 81%.

Several of the studies reviewed used patient responses on either a VAS or NRS where the percentage of the pain reduction in the scores after initiation of treatment was stated or could be calculated.[28,32,33,38–45] An analysis of the study results at one interval of measurement (~3–7 days after treatment was initiated) demonstrated a 20%–71% reduction in the VAS or NRS from the baseline pain assessment. Upon the final interval of measurement, there was a 43%–81% reduction in the VAS or NRS from the baseline pain assessment. The interval length varied among studies but was >7 days after initiation of treatment.

Other studies reported the percentage of the categories considered as adequate pain relief or satisfactory pain intensity by dividing the patients' responses for the VAS, NRS, or VRS into categories. For example, the pain intensity measured by a VAS (0–10 point) might be divided into categories of "none" (0 points), "mild" (1–3 points), "moderate" (4–6 points), and "severe" (7–10 points), where "none" or "mild" pain might be considered as adequate pain relief. Likewise, on a four point VRS, the categories of "none" or "mild" might be considered as adequate pain relief. Results from these studies were reported according to the percentage of patients in each category. Mercadante et al[27] used a VAS and reported that 81% of the patients without incidental pain had "no pain" or "mild pain" at the time of their death, but only 50% of the patients who experienced incidental pain had "no pain" or "mild pain" at the time of their death. Ventafridda et al[34] using a VRS reported that 76% in their sample reported "none" or "slight" pain after 1 month of treatment. Zech et al,[26] in a validation study of the WHO guidelines using a VRS, reported that 72% of the patients had "no pain" or "mild pain" at the time of their death. Tsui et al[44] reported that 88% of their patients were discharged with a VAS of ≤3 (0–10 scale), indicating that the patients experienced "no" pain or "mild" pain. Bhatnagar et al[46] reported that 87% and 90% of patients had good pain relief (VAS <3) at 1 month and 6 months, respectively. Of the studies that reported the percentage of the categories considered as adequate pain relief or satisfactory pain intensity by dividing the patients' responses for the VAS, NRS, or VRS into categories, 50%–90% of the patients experienced adequate pain relief.

Similar to other studies that categorized the degree of pain intensity, Takeda[47] categorized the degree of pain reduction of patients' responses on the VAS into three levels: complete relief (no pain), acceptable relief (>90% relief of pain or reduction of the scores), and partial relief (decrease in severity of pain, but a reduction of <90%). At the end of an unknown duration of treatment, 97% of the sample reported complete (86%) or acceptable (11%) relief from pain. Inclusion of the percentage of the categories considered as adequate pain relief determined by Takeda[47] into the range compiled from the other studies that reported the percentage of the categories considered as adequate pain relief ("none" or "mild" pain) indicates that 50%–97% of the patients experienced adequate pain relief.

Unlike studies that reported the percentage of VAS reduction of pain, Minotti et al[35] and Keskinbora et al[31] reported patients' mean scores of pain intensity using the VAS after treatment only. These studies did not report pain levels before the introduction of the WHO guidelines. One of the inclusion criteria for the studies, however, was that patients' scores of pain using the VAS (0–100 points) were >40 or the NRS >4 (0–10 points). After 7 days of treatment, Minotti et al[35] reported that the mean of the patients' scores using the VAS was <40. Keskinbora et al[31] demonstrated graphically that the patients treated with an adjuvant in addition to an opioid experienced a mean pain of <4 on days 4 and 13 after initiation of treatment with the WHO guidelines. The reduction in pain was statistically significant between patients who received an opioid and an adjuvant and those

patients who received an opioid only for their cancer pain. The percentage of reduction in pain intensity was not provided and could not be calculated from information provided within the two studies.

Siguan et al[48] used a pain reduction scale (PRS) to survey the patients with cancer pain. With this scale, the respondents had the option of indicating whether they had 0%, 25%, 50%, 75%, or 100% pain relief. At the end of an unreported duration of treatment, 86% of respondents stated that they had at least a 75% pain reduction and 96% had at least a 50% pain reduction. Similarly, Vielvoye-Kerkmeer et al[49] had respondents rate the effectiveness of their treatment as "poor", "moderate", "good", or "excellent". In their study, 69%–71% of patients rated their pain relief as "good" or "excellent".

Zech et al,[26] Meuser et al,[41] and Maltoni et al[30] used other methods of evaluating effectiveness of treatment with the WHO guidelines. In addition to reporting the patients' mean pain scores of the VAS or NSR at baseline and after treatment, the first two studies also categorized pain relief according to the number of days the patient experienced severe pain. Thus, if the patient reported their average pain to be severe, very severe, or maximal on <10% of days, treatment effectiveness was defined as "good"; on 10%–30% of days as "satisfactory"; and on >30% of days as "inadequate". With these categories, Meuser et al[41] found 86% of the patients and Zech et al[26] found 88% of the patients experienced "good" or "satisfactory" pain relief effectiveness. A third study by Maltoni et al[30] described the percentage of days with worst pain that was ≥5 on the NRS (0–10 points). Maltoni et al[30] reported that on 9%–29% of the days, patients experienced moderate-to-severe pain. Using the criteria from Zech et al[26] and Meuser et al,[41] 100% of the patients in the study by Maltoni et al[30] experienced "satisfactory" or "good" treatment effectiveness with the WHO guidelines. The range of the pain relief effectiveness of the three studies ranged from 86% to 100%.

In the reviewed studies, the overall effectiveness of the WHO Cancer Pain Relief guidelines was found to range from 20% to 100%. The effectiveness identified in the majority of the studies was >50%. The broad range of effectiveness is dependent upon many measurement factors, including the intensity of the pain, the pain instrument used, the duration of treatment, and the outcome variable of pain relief/control.

Discussion

The overall literature rating is suggestive of a relationship between the WHO guidelines and pain relief. Evidence from research indicates 20%–100% of patients with cancer pain – considering their status of treatment or end-of-life care – can be provided adequate pain relief with application of the WHO guidelines, with a majority of studies identifying relief >50%.

Various means of reporting outcomes were used. A reduction of 57%–81% was reported using patient responses with the IPS after treatment with the WHO guidelines. The NRS and VAS were reportedly reduced in the range of 20%–81% after treatment across levels of severity of pain. Studies that placed patients' responses into categories that described the pain intensity experienced reported that 50%–90% of the patients experienced "none" or "mild" pain after treatment with the WHO guidelines. Other studies reported that the mean intensity experienced by patients was <4 or 40 (depending on whether scale was based upon 0–10 points or 0–100 points), indicating full effectiveness of the WHO guidelines. Other studies reported that 69%–86% of the patient responses indicated that patients experienced at least 75% pain relief or felt that their pain control was "good" or "excellent" after treatment. Effectiveness of the WHO guidelines was reported between 86% and 100% for patients who were experiencing "severe", "very severe", or "maximal" pain on 0%–30% of the treatment days. This review demonstrated that pain could be reduced or eliminated in a great majority of the patients when they receive treatment based on the WHO guidelines.

No other guidelines have had the profound effect on cancer pain as the WHO guidelines.[12,50,51] Because only one study met inclusion criteria after 2008, it is questioned whether this finding indicates recognition of the WHO guidelines, and hence a decreased need for publications of their effectiveness or the acceptance of the treatment of cancer pain with opioids.[32] The timeframe correlates with the publication of the European Association for Palliative Care guidelines[52,53] and the American Pain Society guidelines for cancer pain treatment.[54,55] These agency guidelines have recognized the worldwide problem of cancer pain, combined with the increasing availability of different opioids, opioid preparations, and interventional procedures during the last 20 years. These agencies have tried to update the international guidelines on the management of cancer pain while focusing on the role of opioids. The WHO guidelines, though not as specific in direction, encompass a clear and simple approach that has an educational value and is easily remembered and disseminated. Regardless of the age of the WHO guidelines, they still are the cornerstone for cancer pain treatment worldwide. Unfortunately, many practitioners are

not using the WHO guidelines and some do not know what the WHO guidelines entail.[56,57] The clear message resonating from the effectiveness of the WHO guidelines is that they are an effective and cost-effective means to provide cancer pain relief.

Limitations

In the reviewed studies, it was not always specified whether the WHO analgesic ladder or the entire WHO guidelines were being investigated. The language regarding the usage of the ladder or the full guideline was often not stated. Five studies treated patients with the ladder only or eliminated the study participants who underwent additional treatment that might affect pain perception. Eleven of the reviewed studies included patients who were also being treated with antineoplastic treatment, intrathecal analgesics, neurolytic procedures, or surgical procedures, while others did not specify if the patients underwent additional treatment. As the WHO guidelines endorse the use of other treatment modalities than the analgesic ladder if needed, the guidelines should be investigated in its entirety. Some experts suggest that the WHO analgesic ladder has a fourth and/or fifth step that may include a step for interventional procedures, including nerve blocks, neurolytic blocks, spinal stimulators, and epidurals[11,12,58] or a step for opioid switching that includes both pain and side effects as criteria for switching analgesics.[59] It can be argued that having the interventional nerve blocks at a later step implies they should be used last. Evidence exists that the nerve blocks may be more effective if considered earlier.[60,61] Thus, like adjuvant analgesics, they may need to be considered at any step and so may need to be placed alongside the ladder rather than a separate step.

Summarization of the studies proved to be challenging due to different methods of measuring pain, variations in defining the acceptable levels of treatment effectiveness, and missing data. Multiple instruments with different scales and values described pain intensity. Pain intensity was rated according to IPS, VAS, NRS, VRS, and PRS. Particularly, the use of the IPS made it very difficult to compare pain treatment effectiveness between studies since a score of 20 may indicate a range of severe pain for 2 hours or mild pain for 20 hours. Since duration and intensity were a combined score, this type of scoring made it unfeasible to compare the pain treatment effectiveness with other studies and to determine whether adequate treatment effectiveness was achieved. Similarly, reporting pain relief according to the number of days the patient experienced severe or very severe pain made comparisons unrealistic. Even the same type of scale may have had multiple interval labeling systems associated with them. For instance, the VRS may have had four or six points. The variability in the methods of measuring pain or pain treatment effectiveness made comparisons difficult.

Moreover, the studies reviewed categorized the results according to various operational definitions of adequate or inadequate pain treatment effectiveness. This review categorizes adequate treatment effectiveness as the pain intensity as being 1) less than moderate, 2) a VRS or NRS as $\leq$3 (or 30 on a 0–100 point scale), or 3) a decrease in the pain intensity/increase of pain relief by 70% or more. In addition, some data were not reported in the reviewed studies, which may have made comparisons easier. A more accurate comparison could have been made if data from all instruments had been discussed.

Many studies had high exclusion and/or attrition rates. For instance, in Ventafridda et al,[34] 64% and 31% of the cases in the two groups investigated in the study had to be excluded from the study due to incomplete data collection, incomplete recording of patient assessment, or inappropriate timeliness in the follow-up. Incomplete data collection also was problematic in other studies.[36,42] Given the population studied, some reasons for attrition were death,[27,34,36,38,41,48,49] ineffective analgesia,[35] intolerable side effects,[35,48,49] as well as lost to follow-up,[26,28,33,34,36,41,48] pain absence or resolution,[33,41] low patient compliance,[28,41] change of therapy,[35] patient being treated by another practitioner or facility,[28,41,48] discharged,[36] financial constraints,[48] physician error,[48] and patient receiving other treatments.[35,41]

Although it can be concluded that management of cancer pain as recommended by WHO is effective for a majority of patients, the research designs of the studies in the literature review were retrospective, descriptive, and/or quasiexperimental rather than randomized controlled trials (RCT). A relationship between these two factors is consistent with the knowledge generated in prior pain relief investigations, as it is a combination of pain management knowledge acquired through multiple sources that is being tested with the WHO guidelines. Although the relationship between WHO guidelines and pain relief is plausible and likely, the predictive quality of experimental designs with RCT is missing, and the subsequent ability to predict the effectiveness of the WHO guidelines through evidence-based certainty is lacking.[11]

Additional methodological limitations other than design are noted. Because of the population, most studies of oncology patients employ convenience samples, and thus, findings are not generalizable. For example, it is possible for patients with cancer who are hospitalized to more likely be

experiencing severe pain than those who are not hospitalized. Similarly, some studies included patients with severe pain only.[27,30,31,49] Achieving adequate pain relief may be more difficult in more severe cases. Therefore, the studies measuring the effectiveness of the WHO guidelines in reducing the intensity of cancer pain in hospitalized patients or patients who are only experiencing severe pain cannot be generalized to all patients with cancer.

Many of the samples were drawn from one institution in one country. Sampling populations from one institution and generalizing the findings globally are inappropriate as several other factors such as availability of different opioids may affect the adequacy of pain relief. Furthermore, many studies included only patients treated by cancer specialists; patients treated by practitioners without oncology training may be more likely to experience inadequate pain relief. The convenience samples in these studies may produce different findings than a randomized sample from a large, international cancer pain patient population.

In the reviewed studies, the sample sizes of persons with cancer pain vary, but many samples are small. The results from this limited sample size, especially with convenience sampling, may differ from the population. As with drawing from one-institution samples, the small samples may allow some variables to affect the results, such as the practitioner, local practices and beliefs, and economic or social influences. With small sample sizes, a few patients who improved dramatically while receiving care utilizing the WHO guidelines may alter the mean improvement of the group even if other patients perceived little or no benefit with treatment. Small sample sizes, especially combined with convenience sampling, render widespread generalizations inappropriate.

Other methodological problems with measuring cancer pain can be revealed in this review. In longitudinal studies of cancer pain, maturation occurs over time as the disease progresses. It may be difficult to demonstrate an effect of an intervention to decrease incidence and intensity of pain as the pain changes with disease remission or progression. In addition, longitudinal data collection intervals varied greatly. The length of time between data point assessments following implementation of the WHO guidelines and the length of follow-up varied between having only one additional assessment at 1 week after treatment to recording data until death, which may entail follow-up for several months. Testing effects may also be prominent, as many studies did not identify the ability of those who collected the data. Overall, the multiple methodological problems identified potentially lead to less accuracy in the individual study results and makes comparisons between studies difficult.

In reviewing the literature, several of the studies operationally defined adequate pain relief as experiencing moderate pain or less pain. Although complete relief is the goal of cancer pain management; sometimes, it is not possible. An acceptable level of pain should be below moderate pain. With moderate or greater pain, there are often marked negative changes in physical or emotional functioning that interferes with the patient's quality of life.[15,62,63] Therefore, the delineation of adequate pain relief should be within the mild or no pain categories.

In order to measure pain and compare results more consistently, a well-established, international pain measurement instrument needs to be used. Difficulty is encountered when comparing various pain intensity measurements as it is unknown whether methods of measuring pain and reporting pain relief affect the results of studies. For example, a difference between an individual's responses on VRS may not correlate with responses on a pain relief scale. Future studies are needed to correlate these measures.

Additional research also is needed to compare methods of reporting pain relief between those reported from pain intensity scales to pain relief scales. Likewise, it is understandable that not only the intensity but also the duration of pain needs to be measured, but placing these two concepts in one index, such as done in the IPS, may cause misinterpretation of the effects of the pain experience on the patient. Perhaps, reporting the intensity and duration in addition to the IPS might be more informative.

The number of points on a VRS and the terms used on the scale need to be standardized so that findings between studies can be compared. The standardized VRS should then be correlated with the NRS so the findings with the two different types of scales can be compared more consistently. Finally, in order to have more accurate results and be able to compare studies, the patient rather than medical personnel or family should complete the pain measurement instruments. Standardization in pain management instrumentation and in its completion would allow more consistent measurement, reporting, and comparison between future studies.

New studies using experimental designs with randomized control groups would support the strength of the relationship between the WHO guidelines and cancer pain relief. According to Oxman et al,[64] WHO recommendations are usually not based on systematic reviews of the literature but rely heavily on experts in a particular specialty such as cancer pain management. Since the release of the WHO guidelines,

a lack of rigor in studies, especially in methodological design, contributes to limitation in generalizability of the published results.[11] Debates regarding the effectiveness of the WHO guidelines remain due to the lack of RCTs. Although RCTs demonstrating a relationship between the WHO guidelines and cancer pain relief are conspicuously absent, there were no evidence-based alternatives supported by RCTs found in the literature that were superior to the WHO guidelines.

The first debate about the effectiveness of the guidelines revolves around the utility of Step 2 of the WHO ladder.[11,65] Proof of the effectiveness of weak opioids is lacking, especially since a limitation of using weak opioids is that there is a ceiling effect.[11] A ceiling effect occurs when an increase in dose does not produce a decrease in pain. In an attempt to avoid using weak opioids, Nunes et al[32] found that a higher incidence of adverse effects occurred when the second step of the ladder was omitted and patients were administered morphine initially. Thus, Step 2 may still be warranted, and future research is needed to explore its value.

A second debate of Step 2 includes the role of nonsteroidal anti-inflammatory drugs.[11] These medications may affect the gastrointestinal tract, platelets, and kidneys, resulting in negative side effects and possible toxicity. A third debate of Step 2 is the lack of criteria for switching from morphine to another opioid, including equianalgesic dosing and the choice of the subsequent opioid to be used.[11,66] A fourth debate is that there are multiple new medications and new formulations of older drugs that need to be investigated that considers their pharmacodynamic and pharmacokinetic properties in patients experiencing cancer pain. Finally, adverse effects of these opioids need to be documented within the RCTs that explore them.

Suggesting rigorous RCTs challenges researchers, including the WHO, to optimize and improve the guidelines or develop alternatives to ensure the highest possible proportion of patients with cancer pain experience pain relief. Nonetheless, the implementation of RCT in studies of cancer pain management is not likely due to ethical and logistic reasons. First, to obtain accessibility to patients with cancer pain, convenience samples are often used. Second, the ability to control for extraneous variables in studies among international health care practices makes coordination of standards difficult for group comparisons. Third, a humane responsibility exists to provide optimal pain relief to all patients, and this renders a control group as being potentially ethically irresponsible. Fourth, given the publication of the WHO guidelines, it is unlikely that the treatment of a potential control group would not be influenced by the broad dissemination of the guidelines that has already occurred. Finally, experts in cancer pain management believe that the effort and expense of experimental studies with control groups is unwarranted.[67,68] This is based on the strength of the fundamental knowledge underlying the guidelines and the acceptance of these principles. Suggesting experimental designs with control groups is an ideal rather than a practical prospect in the actual environment of cancer pain management. RCTs are needed, however, when the effect and differences are smaller such as when comparing various drugs or routes.[67] Comparison groups, gleaned from those treated in various environments, for example, where certain medications are not readily available, would allow for comparison of groups of patients with cancer. Also, data from those treated in the past decade or earlier could be compared to those treated currently.

Cluster randomization is a possible alternative to overcome some of the challenges in getting RCTs regarding cancer pain relief. A cluster randomized controlled trial (CRT) is a type of RCT where groups of subjects and not individuals are randomized. The units of randomization are varied and can be clinics or hospitals, among others. Advantages include the ability to compare drugs head-to-head within the same class rather than with placebos.[69] CRT may relieve issues related to recruitment and self-selection and randomization of patients, thus allowing data collection and availability of results more quickly.[69] The disadvantages to CRTs are the multitude of design choices and stratification of the groups.[70] The need for informed consent may be averted if the drug studied is the preferred drug in the cluster formulary, and so, ethical requirements for CRTs may need to be analyzed and modified.[69]

Several recent studies indicate inadequate cancer pain relief still exists, but these studies also fail to indicate if the WHO guidelines were being implemented during treatment.[15] A review of studies by Deandrea et al,[71] that used the PMI, demonstrated that ~43% of patients with cancer pain are undertreated. The PMI compares the intensity/strength of the analgesic treatment according to the WHO Analgesic Ladder with the patients' reported pain. All studies demonstrated a negative PMI, indicating that the cancer pain is undertreated a majority of the time. Deandrea et al[71] identified factors associated with a negative PMI that included publication before 2001; studies conducted in Europe or Asia; studies conducted in countries whose national income per capita was $40,000 per year or less; and patients being cared for in a general setting rather than a cancer-specific setting. Patients being treated by oncology subspecialists, however, have also been inadequately medicated for pain according to the WHO

guidelines.[15,45] Therefore, the use of the WHO guidelines in oncology specialty areas and by the oncologists themselves cannot be assumed. In future studies, the use of the WHO guidelines to treat patients with cancer with pain should be clearly stated, consistently applied, and then evaluated with the PMI. The results of the review by Deandrea et al[71] suggest that the question might be how the WHO Analgesic Ladder is put into practice rather than its effectiveness.

Other methodological considerations would be to increase the sample size, follow a longitudinal design, use multiple institutions/agencies, and use more institution/agencies from within the USA, all of which are lacking. The sample size for future studies evaluating the effectiveness of the WHO guidelines needs to be increased. Five studies in this review had a sample size of <50 subjects, and 13 additional studies had <100 subjects. Weekly, longitudinal studies until study withdrawal would provide additional data to evaluation the effectiveness of the WHO guidelines in continued relief of cancer pain upon progression of the disease. Other cancer care centers need to be surveyed, especially in understudied countries. In the studies reviewed, for example, only part of one sample came from the USA. These considerations would increase the generalizability and reliability of the findings from future studies.

Conclusion

The studies evaluating the effectiveness of the WHO guidelines provide valuable information on the course of cancer pain and its treatment. From these findings, it can be concluded that the WHO guidelines are useful in promoting cancer pain relief. Evidence from research indicates at least 20%–100% of patients with cancer pain can be provided adequate pain relief across the span of their illness, from treatment-to-demise, with the application of WHO guidelines. Recent studies have reported that patients experiencing cancer pain at moderate or greater levels.[2,3] While comparing the results of the recent studies describing the incidence and intensity of cancer pain, it can be assumed that the WHO guidelines have not been as widely adopted as would be expected since their initial release in 1986. The WHO guidelines reflect the knowledge and effectual methods to relieve most cancer pain, but the guidelines are not being adequately employed. Part of the explanation for the lack of adoption of the WHO guidelines is that they may be considered outdated by many because they are not specific to the pharmacological and interventional options used in contemporary pain management practices. The greatest attribute of the WHO guidelines is its simplicity, whereas, a thorough cancer pain guideline results in a complex document that might not be as useful and easy to disseminate. The conundrum of updating the WHO guidelines is to encompass the latest pharmacologic and interventional innovations while maintaining its original simplicity.

At the same time, the patients who have not had their cancer pain adequately relieved, even when the WHO guidelines have been employed, need further consideration in future research. The WHO guidelines have been successful in making pain relief knowledge more globally available, but from a moral and ethical standpoint, these guidelines need to be promoted and examined until adequate pain relief is reported in all possible patients with cancer pain.

Disclosure

The author reports no conflicts of interest in this work.

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