Systematic Review

A Systematic Review of Observational Studies on the Effectiveness of Opioid Therapy for Cancer Pain

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Background: The prevalence of cancer-related pain and residual pain in cancer survivors is high. Opioids serve as the gold standard for treating moderate to severe cancer pain. The evaluation of the effectiveness of opioids in chronic non-cancer pain has shown a lack of effectiveness, or rather weak evidence for some of the drugs. In contrast, in cancer pain, opioids are expected to be very effective. Due to the nature of the disease, there is evidence of a paucity of randomized trials investigating opioid effectiveness in cancer pain on a long-term basis. Consequently, the effectiveness of opioids in managing cancer-related pain warrants further evidence-based review beyond randomized trials, including observational studies and case reports.

Methods: The comprehensive literature search was conducted for the period 1996 through June 2010. Databases for the search included PubMed, EMBASE, Cochrane Reviews, and clinicaltrails.gov, along with reviews and cross references.

Methodologic quality assessment of the observational studies managing chronic cancer pain with opioids was conducted utilizing the Agency for Healthcare Research and Quality (AHRQ) criteria for observational studies. Analysis of evidence included 5 levels of evidence developed by the United States Preventive Services Task Force (USPSTF) ranging from Level I to III with 3 subcategories in Level II. Grading recommendations were based on Guyatt et al's recommendations with 6 levels: 3 in the strong category and 3 in the weak category.

Results: This evaluation is of 18 manuscripts considered for inclusion; 7 manuscripts met the inclusion criteria based on AHRQ quality assessment. Level of evidence for opioid therapy in cancer pain was Level II-3, and recommendations were 1C/strong recommendation based on observational studies, which could change based on future evidence.

Conclusion: This systematic review of observational studies indicates Level II-3 evidence for effectiveness of opioids in cancer pain therapy, with 1C/strong recommendation based on observational studies, which could change based on future evidence.

Key words: Chronic pain, cancer pain, non-cancer pain, randomized trials, observational studies, case reports, opioids, effectiveness

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Cancer is a highly prevalent and serious public health issue, affecting most commonly the elderly, with the average cancer patient aged 65 at first diagnosis (1-3). In North America about one in 3 adults will develop cancer in their lifetime, with about a 50% fatality rate. Cancer is sufficiently prevalent that some individuals will develop more than one type of malignancy, either sequentially or concurrently

(4-9). Cancer is often painful, with pain presenting as a common heralding manifestation of the disease. As cancer progresses, it is more likely to be associated with pain, and the pain is more likely to be severe. A range of epidemiological studies in several countries and practice settings suggest that pain from a wide variety of cancers is present in about one-third of patients receiving cancer treatment and in 60% to 90% with advanced illness (4,9-12). Further, cancer treatment can also cause pain, and cancer pain is commonly classified as being either due to the underlying disease or due to its treatment (9-13). However, cancer patients can also have pain from non-cancer related conditions, and the causes and prevalence are similar to pain in patients without a cancer diagnosis (14-17).

Commonly, patients with solid tumor malignances present with an asymptomatic mass; less than 50% of patients with non-metastatic disease describe pain from their cancer (4). Cancer can present clinically in a wide variety of ways, with multiple neurological, pulmonary, and gastrointestinal symptoms and signs, but pain is the first symptom of cancer (1-4). Further, there is a tendency for the cancer to be more advanced, and perhaps for this reason, pain can be an independent predictor for full survival.

Inadequate treatment of chronic cancer pain persists despite decades of efforts to provide clinicians with information about analgesics and pain-relieving techniques (13-48). The factors contributing to the undertreatment of cancer pain in the United States have been due to patient-related factors (underreporting, fear of disease progression, poor compliance with prescribed medications), and physician-related issues (legal issues with misuse, abuse, overuse of prescription medications, difficulty assessing pain complaints, lack of information, or lack of expertise) (18-52).

Comprehensive cancer care encompasses a continuum that progresses from disease-oriented, curative, life-prolonging treatment through symptom-oriented, supportive, and palliative care extending to terminal-pace hospital care. Pain management is, and should be, an integral component of comprehensive cancer care (13).

In 1986, the World Health Organization (WHO) established guidelines for treating cancer pain using a 3-tier ladder algorithmic approach (51). Opioids serve as the gold standard for treating moderate to severe pain. In 2008, the American Society of Interventional Pain Physicians (ASIPP) published guidelines for the opioid management of chronic non-cancer pain (53). It concluded that for long-term opioid therapy of 6 months or longer in managing chronic non-cancer pain, there was weak evidence for morphine and transdermal fentanyl in reducing pain or improving function. A systematic review (54) basically showed a lack of evidence for opioids in treating chronic non-cancer pain. In contrast to non-cancer pain, cancer pain is based on a separate paradigm. Most of the shortcomings of managing non-cancer pain with opioids are based on effectiveness data being derived from acute and cancer pain, rather than chronic non-cancer pain (54-64). However, opioids' effectiveness for cancer pain has been evaluated in multiple randomized trials and systematic reviews (65-81), but these trials were done with short-term follow-up and a small number of patients. The effectiveness of opioids in managing cancer-related pain warrants further evidence-based review beyond randomized trials. In contrast to chronic non-cancer pain, which has been criticized for excessive opioid use, misuse, abuse, diversion, and deaths (82-111), cancer pain has more likely been described as undertreated, with minimal problems of abuse, misuse, and diversion (18-51,112).

The goal of this review is to provide an updated assessment of the current literature for evidence-based criteria for the overall effectiveness of opioid therapy in managing cancer pain.

Methods

The methodology utilized here follows a systematic review process derived from evidence-based systematic review and meta-analysis of randomized trials and observational trials (113-124), Consolidated Standards of Reporting Trials (CONSORT) guidelines for the conduct of randomized trials (125-127), and STROBE guidelines for observational studies (128,129).

Literature Search

A comprehensive search of the literature was conducted for the period 1996 through June 2010. Databases for the search included PubMed, EMBASE, Cochrane reviews, and clinicaltrials.gov. The search also included cross-referencing of bibliographies from notable primary and review articles, and abstracts from scientific meetings and peer-reviewed non-indexed journals. The search emphasized opioid therapy in managing cancer-related pain.

The search was conducted by 2 authors. Any disagreements were resolved by consensus with involvement of a third author.

Criteria for Studies Considered for Review

Observational studies involving adult participants at least 18 years of age being treated for cancer-related pain of any duration with any opioid, administered by any route with or without concomitant ancillary medica-

tions, as prescribed within the WHO analgesic ladder were considered. A minimum follow-up period of 3 months was required. The primary outcome measures were efficacy of pain relief and overall safety. Secondary measures were quality of life indicators and psychological improvement.

All studies were reviewed by 2 authors to evaluate inclusion criteria. Any disagreements were resolved by consensus with involvement of a third author.

Methodologic Quality Assessment

The quality and validity of each article comprising this analysis were assessed under the Agency for Healthcare Review and Quality (AHRQ) criteria for observational studies (Table 1) (130) with consensus-based

Table 1. *Modified AHRQ quality assessment criteria for observational studies.*

CRITERION	Weighted Score (points)
1. Study Question • Clearly focused and appropriate question	2
2. Study Population	8
• Description of study population	5
• Sample size justification	3
3. Comparability of Subjects for All Observational Studies	22
• Specific inclusion/exclusion criteria for all groups	5
• Criteria applied equally to all groups	3
• Comparability of groups at baseline with regard to disease status and prognostic factors	3
• Study groups comparable to non-participants with regard to confounding factors	3
• Use of concurrent controls	5
• Comparability of follow-up among groups at each assessment	3
4. Exposure or Intervention	11
• Clear definition of exposure	5
• Measurement method standard, valid and reliable	3
• Exposure measured equally in all study groups	3
5. Outcome Measures	20
• Primary/secondary outcomes clearly defined	5
• Outcomes assessed blind to exposure or intervention	5
• Method of outcome assessment standard, valid and reliable	5
• Length of follow-up adequate for question	5
6. Statistical Analysis	19
• Statistical tests appropriate	5
• Multiple comparisons taken into consideration	3
• Modeling and multivariate techniques appropriate	2
• Power calculation provided	2
• Assessment of confounding	5
• Dose-response assessment if appropriate	2
7. Results	8
• Measure of effect for outcomes and appropriate measure of precision	5
• Adequacy of follow-up for each study group	3
8. Discussion • Conclusions supported by results with possible biases and limitations taken into consideration	5
9. Funding or Sponsorship • Type and sources of support for study	5
TOTAL SCORE	100

Adapted and modified from West S et al. Systems to Rate the Strength of Scientific Evidence, Evidence Report, Technology Assessment No. 47. AHRQ Publication No. 02-E016 (130).

weighted scoring developed by the guidelines committee of ASIPP, which was utilized in multiple previous evaluations (131-147).

Only studies scoring at least 50 of 100 with the weighted scoring criteria were utilized for analysis. Studies scoring 50 to 66 were considered to be of moderate quality and those above 67 were considered to be of high quality.

Each study was evaluated by at least 2 authors for the stated criteria and a third reviewer moderated any disagreements. Any conflict of interest with the reviewed manuscript pertaining to authorship required the involved author not to review the manuscript for quality assessment, clinical relevance, evidence synthesis, or grading of evidence.

Data Abstraction and Management

At least 2 reviewers independently extracted data. Any discrepancies were settled by consensus agreement. Data were analyzed for all conditions of cancer-related pain treated by any route of opioid administration.

Meta-analysis was performed if at least 10 studies were identified meeting inclusion criteria. Meta-analysis in observational studies with less than 10 studies is considered inappropriate as it fails to provide significant effect size and confidence intervals. In the past, it was determined that at least 5 studies were required for randomized trials, thus we have estimated this to be 10.

Analysis of Evidence

Analysis was conducted using 5 levels of evidence, ranging from Level I to III with 3 subcategories in Level II, as illustrated in Table 2 (148) developed by the United States Preventive Services Task Force (USPSTF).

Recommendations

Grading recommendations are based on Guyatt et al's criteria with 6 levels, 1A-1C/strong and 2A-2C/weak, as illustrated in Table 3 (149).

Results

Figure 1 gives a flow diagram illustrating the results of the literature search for opioid therapy in cancer pain.

Methodologic Quality Assessment

Of the 18 studies considered for inclusion (150-167), 7 studies met the inclusion criteria for methodologic quality assessment (150-156) with at least 50 participants and at least 3 months of follow-up. Either sample size and/or duration of follow-up were the primary limiting factors for meeting the inclusion criteria established for the review (157-167). Meta-analysis was not performed due to the lack of a sufficient number of studies meeting inclusion criteria.

Table 4 illustrates the quality assessment scoring of AHRQ criteria for each of the 7 studies (150-156). The quality assessment scores ranged from 62 to 75. Thus all studies met the inclusion criteria for evidence synthesis: a score equal to or greater than 50.

Study Characteristics

Table 5 illustrates the descriptive characteristics of the opioid therapy studies evaluating cancer pain included in the methodologic quality assessment.

The 7 studies meeting the inclusion criteria for this review (150-156) varied in their orientation and focus in dealing with opioid therapy in cancer pain. Research issues pertaining to novel opioid delivery systems, additive analgesic effects, multimodal therapy, comparative

Table 2. *Modified quality of evidence developed by USPSTF.*

I:	Evidence obtained from at least one properly randomized controlled trial or multiple well-conducted diagnostic accuracy studies .
II-1:	Evidence obtained from well-designed controlled trials without randomization or at least one well-controlled diagnostic study of adequate size.
II-2:	Evidence obtained from at least one properly designed small diagnostic accuracy study.
II-3:	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III:	Opinions of respected authorities, based on clinical experience, descriptive studies, and case reports or reports of expert committees.

Adapted from the U.S. Preventive Services Task Force (USPSTF) (148).

Table 3. *Grading recommendations*.

Grade of Recommendation/ Description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Adapted from Guyatt G et al. Grading strength of recommendations and quality of evidence in clinical guidelines. Report from an American College of Chest Physicians task force. *Chest* 2006; 129:174-181 (149).

opioid analgesic efficacy, and breakthrough cancer pain are all represented in one or more of the studies.

Hanna et al (150) carried out a one-year extension study involving 68 patients with moderate-to-severe chronic cancer pain. The patients had successfully completed a previous short-term equivalence study and their pain had been controlled on a stable dose of medication, either OROS hydromorphone or equivalent controlled-release morphine. Patients on controlled-release morphine previously were started on a dose of OROS hydromorphone equivalent to the dose-stable pain control of morphine. All pain scores were maintained at mild to moderate severity and treatment effectiveness was rated as fair to good throughout the study. Ten patients (14.7%) completed the one year study. Death (22.1%) and disease progression (20.6%) accounted for the most common reasons for not completing the study. Only a small proportion (11.8%) withdrew owing to a lack of efficacy. No formal statistical testing was performed on the data. Pain control was maintained during the one year study with once daily dosing of OROS hydromorphone.

Hanks et al (151) studied the safety and efficacy of using oral transmucosal fentanyl citrate (OTFC) in treating breakthrough pain in 57 patients stabilized on a long-acting opioid for cancer-related pain, but were experiencing up to 4 episodes of breakthrough pain daily. Patients were continued on their usual long-acting opioid to control persistent pain and given access to OTCF, as well as their conventional pain medication. Morphine was the conventional breakthrough pain medication for 84% of patients. An effective dose of

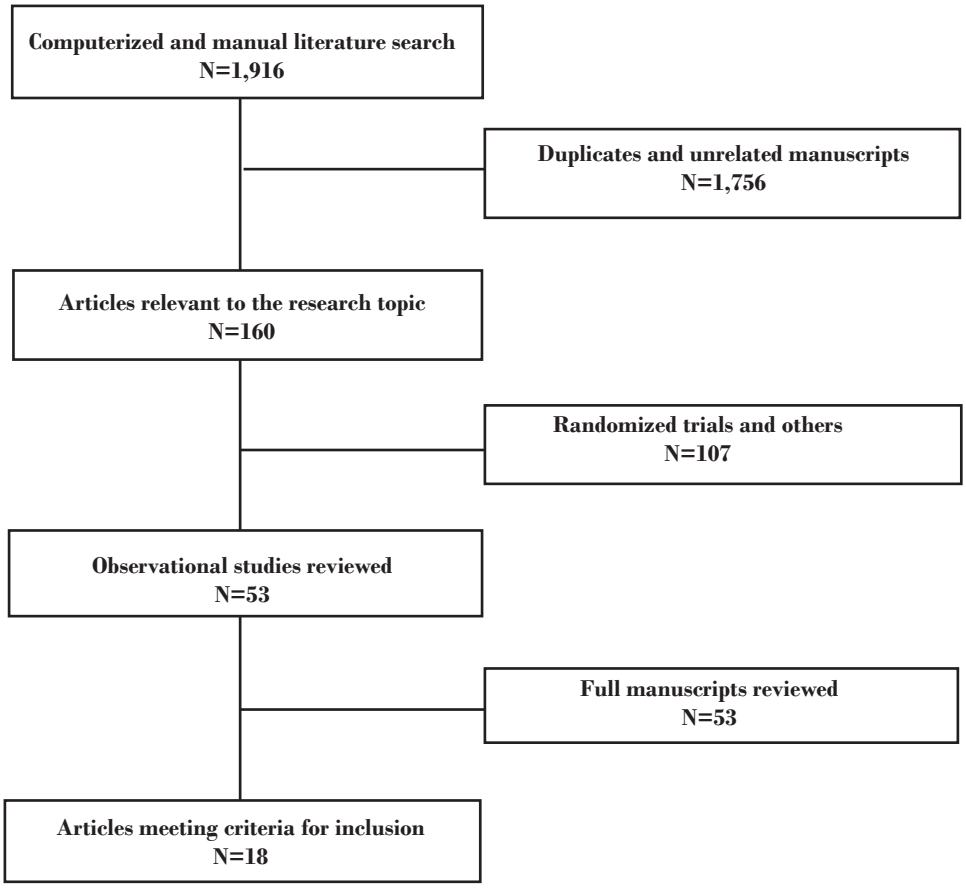

Fig. 1. *Flow diagram illustrating literature search and evaluation.*

OTFC was achieved in 77% of patients. Only 12 patients completed the 6 months of treatment. Comparing OTFC to conventional breakthrough pain medications, OTFC had significantly higher pain relief scores and global medication performance ratings. OTFC was found to be an effective and safe alternative to other opioids in treating breakthrough pain.

Mercadante et al (152) studied the effectiveness of intrathecal morphine in opioid-tolerant advanced cancer pain patients, who were unresponsive to multiple trials of systemic opioids. Inclusion criteria were previous trials with at least 3 opioids and 2 routes of administration. Mean opioid dosing in oral morphine equivalents prior to starting intrathecal therapy was 466 mg/day. Fifty-five patients were selected for intrathecal treatment. A combination of morphine and levobupivacaine was used. The initial morphine dose was calculated from the previous opioid consumption using an oral-intrathecal ratio of 100:1. Complete data with adequate follow-up until death were obtained for 45 patients. Statistically, P values < 0.05 were considered significant. Statistical differences in daily morphine dosing were noted initially, while further increases were not significant. Levobupivacaine dosing did not change significantly.

A large number of patients (n = 589) were studied by Mystakidou et al (153) for an extended period of up to 24 months. Their study examined the safety and efficacy of transdermal therapeutic system-fentanyl (TTS-F) in opioid naïve and opioid intolerant groups with moderate-to-severe cancer pain. The mean duration of participation for the entire population was 9

Table 4. *AHRQ quality assessment criteria for observational studies.*

Criterion	Weighted Score	Hanna et al 2009 (150)	Hanks et al 2004 (151)	Mercadante et al 2007 (152)	Mystakidou et al 2003 (153)	Moselli et al 2010 (154)	Apolone et al 2009 (155)	Weinstein et al 2009 (156)
1. Study Question	2	2	2	2	2	2	2	2
• Clearly focused and appropriate question	2	2	2	2	2	2	2	2
2. Study Population	8	5	5	5	5	5	5	5
• Description of study population	5	5	5	5	5	5	5	5
• Sample size justification	3	0	0	0	0	0	0	0
3. Comparability of Subjects for All Observational Studies	22	14	14	13	14	14	14	14
• Specific inclusion/exclusion criteria for all groups	5	5	5	5	5	5	5	5
• Criteria applied equally to all groups	3	3	3	3	3	3	3	3
• Comparability of groups at baseline with regard to disease status and prognostic factors	3	3	3	2	3	3	3	3
• Study groups comparable to non-participants with regard to confounding factors	3	0	0	0	0	0	0	0
• Use of concurrent controls	5	0	0	0	0	0	0	0
• Comparability of follow-up among groups at each assessment	3	3	3	3	3	3	3	3
4. Exposure or Intervention	11	10	11	10	10	11	11	11
• Clear definition of exposure	5	5	5	5	5	5	5	5
• Measurement method standard, valid and reliable	3	2	3	2	2	3	3	3
• Exposure measured equally in all study groups	3	3	3	3	3	3	3	3
5. Outcome Measures	20	13	13	13	13	13	11	15
• Primary/ secondary outcomes clearly defined	5	5	5	5	5	5	5	5
• Outcomes assessed blind to exposure or intervention	5	0	0	0	0	0	0	0
• Method of outcome assessment standard, valid and reliable	5	3	3	3	3	5	3	5
• Length of follow-up adequate for question	5	5	5	5	5	3	3	5
6. Statistical Analysis	19	5	10	8	12	8	12	10
• Statistical tests appropriate	5	5	5	5	5	5	5	5
• Multiple comparisons taken into consideration	3	0	3	3	3	3	3	3
• Modeling and multivariate techniques appropriate	2	0	2	0	2	0	0	0
• Power calculation provided	2	0	0	0	2	0	2	2
• Assessment of confounding	5	0	0	0	0	0	2	0

Table 4 (cont.). *AHRQ quality assessment criteria for observational studies.*

Criterion	Weighted Score	Hanna et al 2009 (150)	Hanks et al 2004 (151)	Mercadante et al 2007 (152)	Mystakidou et al 2003 (153)	Moselli et al 2010 (154)	Apolone et al 2009 (155)	Weinstein et al 2009 (156)
• Dose-response assessment if appropriate	2	0	0	0	0	0	0	0
7. Results	8	7	8	6	8	7	7	8
• Measure of effect for outcomes and appropriate measure of precision	5	4	5	3	5	5	5	5
• Adequacy of follow-up for each study group	3	3	3	3	3	2	2	3
8. Discussion	5	4	5	5	5	5	5	5
• Conclusions supported by results with possible biases and limitations taken into consideration	5	4	5	5	5	5	5	5
9. Funding or Sponsorship	5	5	0	0	0	0	5	5
• Type and sources of support for study	5	5	0	0	0	0	5	5
TOTAL SCORE = 100	100	65	68	62	69	65	72	75

Adapted and modified from West S et al. Systems to Rate the Strength of Scientific Evidence, Evidence Report, Technology Assessment No. 47. AHRQ Publication No. 02-E016 (130).

Table 5. *Study characteristics.*

Study/Methods	Participants	Interventions	Outcomes	Results	Conclusions
Hanna et al (150) 2009 Phase III, open-label, single treatment arm, one year extension study. AHRQ score: 65/100	68 patients with moderate-to-severe chronic cancer pain.	OROS, a sustained-release oral formulation of hydromorphone given once daily with dosing adjustments as needed; mean dose 43.7 mg/d.	Efficacy end points: BPI scores, BPI interference scores at baseline and endpoint; and patient/investigator global evaluations at one month and endpoint.	Pain relief, BPI scores slightly worsened at end point compared to baseline. Mean BPI interferences scores slightly worsened from baseline to endpoint for each QoL item measured. Global evaluation scores also worsened over the course with treatment effectives rated as fair to good.	Most efficacy measures were maintained up to at least one year with once daily dosing of OROS hydromorphone in patients with moderate-to-severe cancer pain.
Hanks et al (151) 2004 Open, multicenter, prospective study. AHRQ score: 68/100	57 patients with cancer-related pain, stabilized on a long-acting opioid, but experiencing up to 4 episodes of BTP daily; max duration of treatment 6 months.	OTFC was added to a stable long-acting opioid regimen for treating BTP; OTFC dosing was tritrated up until it effectively treated episodic BTP.	Efficacy in pain intensity/ pain relief and global performance of medication with OTFC vs. previous conventional medication; adverse effects profile.	Significantly higher PID, TOTPAR and global medication performance scores with OTFC vs. conventional medications at all measured times; adverse effects were mild, typical for opioids, none serious or unpredictable.	OTFC is an effective and safe alternative to other opioids in treating BTP.
Mercadante et al (152) 2007 Prospective cohort study AHRQ score: 62/100	55 advanced cancer patients, highly opioid tolerant with adverse side effects and poor pain control.	IT morphine and levobupivacaine infusion. Initial IT morphine dose calculated using a morphine oral-IT ratio of 100:1. Followed up to 4 years or until death.	Pain/symptom intensities using a numerical scale at the start, time of discharge, and at one, 3, 6 month intervals and one week before death.	Statistical differences in pain were noted at different time intervals; statistical decreases in drowsiness and confusion were found until one-month after starting; systemic opioid requirements significantly decreased at all intervals.	IT morphine and local anesthetic infusion provided long-term improvement in analgesia, decreased adverse effects, and lowered systemic opioid consumption.

Table 5 (cont.). *Study characteristics*.

Study/Methods	Participants	Interventions	Outcomes	Results	Conclusions
Mystakidou et al (153) 2003 Open-label prospective trial with 2 parallel groups. AHRQ score: 69/100	589 patients either opioid-naïve or intolerant to morphine with moderate-to-severe cancer pain.	TTS-F initiated in 2 groups: 1. Opioid-naïve starting at 25μg/h; 2. Morphine transfer, mean morphine dose of 122 mg/d, correlated to a mean initial dose of 50 μg/h; TTS-F dose increments of 25 μg/h made according to analgesic requirements. Follow-up over 24 months.	Pain relief, VAS 0-10 scale, QoL assessment, treatment satisfaction, and side effects profile.	Median duration of study participation was 9 months. Statistically significant decreasing pain and improvements in QoL measures and treatment satisfaction in both groups. 90% overall satisfaction for both groups. No significant difference in the side effect profiles between the groups.	TTS-F is effective and well-tolerated for opioid-naïve and morphine transfer patients with cancer pain.
Moselli et al (154) 2010 Prospective observational open-label pilot study. AHRQ score: 65/100	220 consecutive cancer patients requiring opioid CSI.	Ketoprofen added to morphine CSI in 172 patients (SG); 48 received only a morphine CSI (CG).	Measure of efficacy pain relief on NRS; safety measures per the number and severity of adverse effects, after 3 months.	Pain well controlled in 80% of SG vs. 46% in CG. Patients needing to increase the morphine dosage and the relative dose increase was significantly lower in the SG. Typical NSAIDs toxicity was noted in 4.1%.	Ketoprofen in combination with opioid CSI is a safe and effective approach to cancer pain.
Apolone et al (155) 2009 Prospective, nonrandomized, open-label study. AHRQ score: 72/100	398 cancer patients requiring WHO-Level III opioids.	257 patients were using TDS-B at baseline study; 141 were opioid naïve and changed to TDS-B.	Pain characteristics were primary outcome measures; secondary measures included satisfaction with care, QoL, symptoms. 3 month follow-up.	15% of patients had at least a 20% improvement in pain relief; 40% reported an increase in satisfaction; symptoms were tolerable.	TDS-B results were comparable to those of other WHO-Level III opioids.
Weinstein et al (156) 2009 Long-term open-label safety study. AHRQ score: 75/100	232 opioid-tolerant cancer patients with BTP.	120 patients from previous FBT RCTs; 112 FBT-naïve patients titrated to an effective FBT dose. All received concomitant, maintenance opioid analgesics.	Safety and tolerability of FBT; effectiveness in alleviating BTP using AE reports, Global Medication, and Patient Assessment of Medication questionnaires; at least 12 month follow-up.	AEs occurred at higher rates during the maintenance phase; no unexpected AEs occurred; 33% withdrew due to AEs; an effective FBT dose was achieved in 71%; patients favored FBT over previous BTP medication 88% vs. 12%.	FBT is effective, has a favorable safety profile and is well tolerated long-term.

Key: BPI=brief pain inventory; QoL=quality of life; OTFC=oral transmucosal fentanyl citrate; OROS=trade name for sustained-release hydromorphone formulation; VAS=visual analogue scale; IT=intrathecal; TTS-F=transdermal therapeutic system-fentanyl; CSI=continuous subcutaneous infusion; SG= study group; CG=control group; NRS=numerical rating scale; NSAIDs=nonsteroidal anti-inflammatory drugs; AHRQ=Agency for Healthcare Research and Quality; WHO=World Health Organization; TDS-B=transdermal system-buprenorphine; BTP=breakthrough pain; RCT=randomized controlled trials; FBT=fentanyl buccal tablets; AEs=adverse effects; PID=pain intensity difference; TOTPAR=total pain relief

months. There were no significant differences in side effect profiles between the groups. The differences in dose between the 2 groups were statistically different. Overall, 89% of patients were satisfied with their pain relief. Thus, TTS-F provides long-term pain satisfaction with mild side effects in both opioid naïve and opioid intolerant patients.

Moselli et al (154) took a somewhat different approach. Ketoprofen, a non-steroidal anti-inflammatory drug (NSAID), was added to a morphine continuous subcutaneous infusion (CSI) regimen of 172 patients and measures of analgesic efficacy and safety were compared with that of 48 patients receiving morphine CSI alone. Pain was found to be well controlled in 80% of the combined ketoprofen and morphine CSI group compared to 46% with morphine CSI alone. Typical NSAID side effects were noted in only 4.1% of the ketoprofen treated group. This study suggests that multimodal analgesic therapy, in this case the addition of an NSAID, can augment opioid analgesic effect in cancer pain.

Apolone et al (155) addressed the WHO analgesic protocol by introducing a novel analgesic delivery system. In their study, 398 cancer patients requiring WHO-Level III opioids were treated with transdermal system-buprenorphine (TDS-B), which included 141 patients who were opioid naïve prior to starting TDS-B. Outcome measures for pain relief and patient satisfaction were followed for 3 months. Overall results appeared marginal with 15% reporting at least a 20% improvement in pain relief and 40% noting increased satisfaction with their therapy. It was concluded that the results with TDS-B were comparable to those of other WHO-Level III opioids.

Weinstein et al (156) focused their study on the effectiveness and safety of adding another opioid to a stable maintenance opioid regimen for breakthrough pain. Fentanyl buccal tablets (FBT) were added to the analgesic regimen of 232 opioid-tolerant cancer pain patients having significant breakthrough pain. An effective FBT dose was achieved in 71% of patients, while 33% had to withdraw from the study secondary to adverse effects. FBT were found to be effective in treating breakthrough pain and well tolerated long-term during the 12 month follow-up.

Three of the 7 studies reviewed rated AHRQ scores of between 50 and 66 and were considered as moderate quality, while the 4 remaining studies yielded scores above 67 for a high quality consideration.

Effectiveness

All of the 7 observational studies meeting the quality assessment criteria (150-156) evaluating opioid therapy in cancer pain showed positive results for a duration of at least 3 months. Three studies yielded positive results at 12 months follow-up.

Level of Evidence

Analysis of evidence for opioid therapy in cancer pain was Level II-3 for quality of evidence obtained from multiple observational studies.

Recommendation

A grade recommendation based on Guyatt's criteria yields a 1C/strong recommendation based upon the current evidence derived from observational studies with benefits clearly outweighing risks and burdens. This recommendation could change pending future evidence.

Discussion

This systematic review provides results obtained from observational studies encompassing an investigational design, which fulfill the inclusion criteria established for the review. Conventional wisdom has always placed the findings from randomized controlled trials at a higher level of confidence than those from observational studies. The rationale is that observational studies tend to overestimate treatment effects (113,119-124,127,129).

The basis for using randomized trials arises from evidence that based on observational studies, many recommended surgical and medical interventions have later been demonstrated to be ineffective or even harmful (168-172). However, there also has been contradictory evidence demonstrated for RCTs (113,119-124,127,129,173,174). Further, not all questions can be addressed in an RCT and evidence shows that only 40% of treatment questions involving surgical procedures are amenable to evaluation by an RCT, even in an ideal clinical setting (175-178).

In placebo-controlled trials, multiple effects can occur to distort the results, not only limited to placebo or the Hawthorne effect (179,180). The Hawthorne effect is described as changes in clinicians' or patients' behavior because of being observed, improving the results. In contrast, the placebo effect occurs from patients' expectations for benefit (181-186).

In a 2005 publication, Hartz et al (187) assessed observational studies of medical treatments and conclud-

ed that reporting was often inadequate to compare the study designs or allow other meaningful interpretation of results. However, the concept that assigning participants randomly to either experimental or control groups as the perfect science has been questioned (188). While researchers believe that randomization ensures that participating groups will differ only by chance, it does not guarantee that balance will actually be achieved through randomization (169,189,190).

Benson and Hartz (191), in a 2000 publication comparing observational studies and RCTs, found little evidence that estimates of treatment effects in observational studies reported after 1984 were either consistently larger than or qualitatively different from those obtained in RCTs. Further, Hartz et al (192), in assessing observational studies of chemonucleolysis, concluded that the results suggested that review of several comparable observational studies might help evaluate treatment, identify patient types most likely to benefit from a given treatment, and provide information about study features that can improve the design of subsequent observational studies or even RCTs; however, cautioning that the potential of comparative observational studies has not been realized because of concurrent inadequacies in their design, analysis, and reporting. Concato et al (193), in a 2000 publication evaluating published articles in 5 major medical journals from 1991 to 1995, concluded that the results of well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment as compared with those in RCTs on the same topic. In fact, Shrier et al (194) found that the advantages of including both observational studies and randomized trials in a meta-analysis could outweigh the disadvantages in many situations and that observational studies should not be excluded a priori.

Ioannidis et al (195) has shown good correlation between results of randomized and non-randomized trials in their estimates of efficacy in medical interventions, with good correlation of summary odds ratios ($R = 0.75$; $P = <0.001$).

The 7 studies presented as meeting the inclusion criteria for this review (150-156) represents a heterogeneous collection of research concerns in opioid cancer pain therapy. A search of the literature involving opioids in cancer pain revealed numerous observational studies dealing with various aspects of opioid-related cancer pain therapy.

The use of transdermal opioid delivery systems primarily for fentanyl, but also buprenorphine, for treating cancer pain shows promise. In addition to the study by Mystakidou et al (153) and Apolone et al (155), which met inclusion criteria, other studies of shorter duration and fewer participants have shown transdermal fentanyl to be effective and safe.

Sustained-release oral opioid preparations provide the mainstay for analgesic maintenance in cancer pain management. Different types of opioid sustained-release formulations are available and have been shown to be safe and efficacious. In addition to the study by Hanna et al (150), other studies not meeting the review inclusion criteria have reinforced these findings.

The therapeutic challenge of managing breakthrough pain within a cancer pain analgesic regimen was illustrated in studies by Hanks et al (151) and Weinstein et al (156). In both cases an oral preparation of fentanyl formulated to maximize rapid onset with short duration of effect was found to be effective and well tolerated. These types of preparations are intended for adjunctive use with a longer-acting, sustained-release opioid for maintenance therapy. Similarly, other studies falling short of meeting the inclusion criteria have also demonstrated the effectiveness of these opioid formulations.

The concept of multimodal, additive analgesic therapy for cancer pain was addressed in 2 of the included studies. Moselli et al (154) illustrated the additive analgesic effects of combined opioid and NSAID therapy in treating cancer pain. Based upon the WHO cancer pain analgesic protocol, changing the level of treatment to achieve a greater degree of pain control involves the addition of a new class of analgesic to an existing pain regimen. This forms the basis for additive analgesic effectiveness.

The Mercadante et al study (152) was unique in its intrathecal route of opioid administration, as well as its combined additive effect with a local anesthetic, levobupivacaine. The study represented a therapy of last resort for 55 patients with advanced cancer, who were followed for up to 4 years or until death. Results showed long-term improved analgesia with decreased occurrence of the typical opioid adverse effects and an opioid sparing effect. Limitations and deficiencies inherent to the study did, however, result in a low AHRQ score.

Thus, the 7 articles meeting the inclusion criteria for the review (150-156) represent a spectrum of clinical research issues surrounding the current use of opioids in cancer pain therapy. The number of selected studies is small due largely to the nature of the studies re-

viewed and the criteria upon which they were selected. The findings from these studies are, however, supported and validated by many other observational studies, which fall short of the stated inclusion criteria.

Limitations of this systematic review include a paucity of studies evaluating effectiveness of opioids in cancer pain on a long-term basis. Consequently, a paucity not only exists in conducting randomized trials for long-term relief, but also with observational studies.

The future of evidence-based medicine for cancer pain management continues to be poorly addressed, despite the effectiveness of opioids in managing chronic cancer pain rather effectively. Thus, it is essential to conduct randomized and non-randomized trials to establish the efficacy of opioids in managing chronic cancer pain, which will also provide data on the dose responses and treatment of breakthrough pain.

Conclusion

Based on the available evaluation and 7 observational studies, this systematic review of observational studies indicates Level II-3 evidence of effectiveness for opioids in cancer pain therapy with 1C, a strong recommendation; however, this recommendation could change based on further available evidence.

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