The Long-term Analgesic Effectiveness of Opioid Therapy in Chronic Non-Cancer Pain Patients: A Literature Review of Randomized Controlled, Open-label, and Epidemiologic Studies

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INTRODUCTION

- Pain may be the most common reason for seeking medical attention in the United States, and chronic pain can have a profound effect on a person's day-to-day life when it goes under- or un-treated.[1]
- The treatment of patients with pain is multimodal and includes nonpharmacological and interventional approaches along with non-opioid and opioid analgesics. Guidelines and recommendations for the chronic use of opioids have been published from federal government, state agencies and medical societies, including CDC, Washington State and AAPS/AAPM.[2-5]
- Although opioids have represented a mainstay treatment for chronic intractable pain, some argue that the risks of abuse, overdose and death outweigh their purported analgesic benefits. Many state that there is a scarcity of scientific evidence, including a lack of randomized placebo-controlled trials, that demonstrate that opioids are effective "long-term". These statements represent opinion based on meta-analyses and reviews of randomized placebo-controlled trials that found no evidence to support long-term (>3 months) opioid therapy (LOT) for patients with chronic non-cancer pain (CNCP).[6-13]
- This is not surprising because randomized placebo-controlled trials in patients with moderate to severe pain of greater than 3 months duration in patients are challenging for a number of reasons, including difficulty with:
  - Approval – institutional review boards are unlikely to sanction long-term placebo controlled trials for ethical reasons;[14]
  - Recruitment – patients are unlikely to consent to the possibility of being randomized to receive long-term placebo;[14]
  - Retention of subjects – placebo subjects are likely to drop out and skew resulting data.[14]
- However, there is data in patients receiving LOT collected in numerous studies. Long-term trials (≥6 months) including single-arm open-label (OL) studies, open-label extension (OLE) studies, randomized clinical trials (RCTs) that compared different therapies, and epidemiology studies, represent a source of useful information to assess the effectiveness of LOT. These measure longitudinal changes in both pain and functional outcomes.
- The patients in these OL studies and the subset of patients in RCTs that elect to continue into OLE studies may actually reflect the real-world patients who are maintained on LOT.

PURPOSE

- The purpose of this study is to provide an up-to-date review of the literature for all studies of LOT (≥6 months), including RCTs, OL, OLE, and epidemiologic studies, for CNCP patients that include assessments or measure changes in pain scores and function.

METHODS

- We conducted a literature search of published studies of long-term opioid analgesic therapy ≥6 months in duration in CNCP patients. Studies were identified using the search terms "opioid," "long*," and/or "therapy" in Medline, EMBASE, Biosis Previews, and PubMed through March, 2016
- Additional articles were identified through consensus statements, clinical guidelines, literature reviews, and meta-analyses
- For this literature review, four key outcomes were extracted for each study, where available:
  1. Person-years of therapy was either collected directly from study reports or calculated based on the average number of subjects at the beginning and at the end of the study and the length of the study.
  2. Reported changes from baseline to end of study in "pain right now," "average pain," "current pain," or "usual pain" as measured on the Brief Pain Inventory (BPI), 5-point or 11-point numeric rating scale, or 100-mm visual analogue scale were obtained. Percent changes in pain scores from start to end of study were stratified by study duration (6 to <12 months, and ≥12 months) and study type (RCT, OL, OLE, epidemiology). If quantifiable, changes in pain scores for OLE studies from the screening visit preceding the start of therapy to the end of the extension phase were collected.
  3. When available, pain measures in 3-month intervals were determined.
  4. When available, functional health variables, including physical and mental health, were measured by the Short Form 12 (SF-12) and 36 (SF-36) Health Surveys as secondary endpoints.

RESULTS and DISCUSSION

- Two-hundred-sixty-five articles representing 267 studies on long-term opioid therapy were identified. Of these, 82 were not original studies, 2 were published in a language other than English, 43 did not evaluate a chronic noncancer pain (CNCP) population, 63 were less than 6 months in duration, and 7 did not evaluate analgesic effectiveness (Figure 1).
- After exclusions, there were 70 studies included in the current report: 8 RCTs,[15-22] 33 OL trials,[23-55] 14 OLE studies,[56-69] and 15 epidemiology studies,[70-84] of which there were 11 cohort studies,[70-80] and 4 cross-sectional studies.[81-84]
- The 55 studies which includes RCTs, OL studies, and OLE studies represented 13,807 patients and 11,798 person-years of opioid treatment experience. The 15 epidemiology studies represented 5,492 patients and 4,477 person-years of opioid treatment experience

Figure 1. Flowchart of studies included in the current evaluation

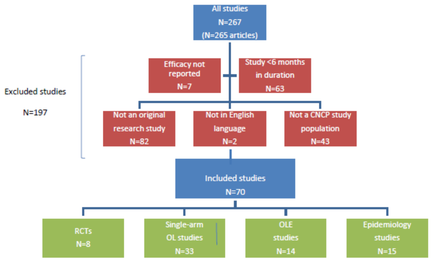
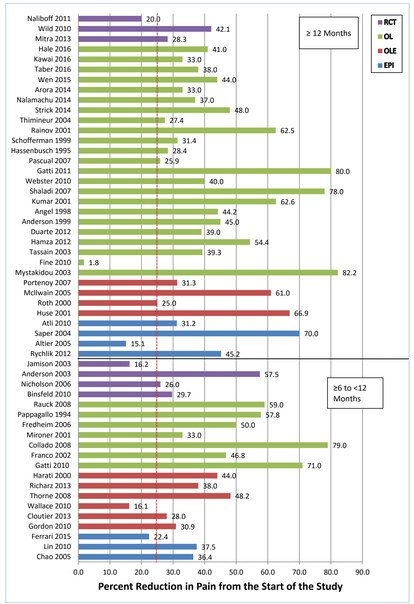


Figure 2. Pain Reduction in RCTs, OL, OLE and Epidemiology Studies ≥ 6 Months duration.
Percent Reduction from Start of Study (or preceding RCT or OL for OLE studies) to End-of-Study in Average, Usual, or Current Pain

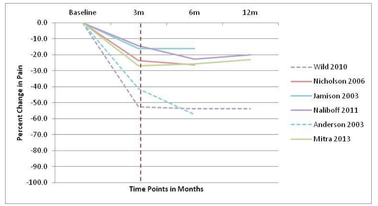


- Fifty-four studies had data for the percent change in pain scores from study baseline to end of study. Of these, 20 were ≥6 to <12 months in duration and 34 were ≥12 months in duration (Figure 2).
  - Among studies ≥6 to <12 months long, 17 (85%) reported an improvement in pain of ≥25% from baseline.
  - Among studies ≥12 months long, 31 (91%) reported an improvement in pain of ≥25% from baseline.
  - Study duration (≥6 to <12 months versus ≥12) had little affect on the proportion of studies demonstrating a ≥25% and ≥50% reduction.
  - Forty-one studies (76%) reported a ≥30% reduction in pain scores.
  - Three studies with some of the smallest analgesic responses, Fine,[50] Naliboff[18] and Altier[76] were conducted in patients who were taking opioids before the start of the study (in Altier[76] 85% of patients were taking opioids before the start of the study).

Changes in Pain Scores Over Time

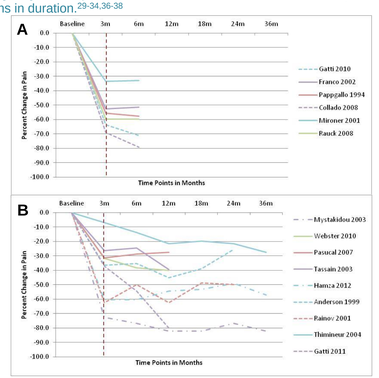
- There were 6 RCTs[15-20] (Figure 3), 16 OL[23-38] (Figure 4A and 4B), and 8 OLE[56-63] (Figure 5) studies that reported pain scores over 3-month intervals.

Figure 3. Percent change in average, usual, or current pain scores over time among RCTs[15-20]



- These RCTs were not placebo-controlled but compared different analgesic therapies to each other.
- In each of these studies, opioid therapy produced an initial decrease in reported pain that was maintained to the end of the trial at 6 or 12 months.

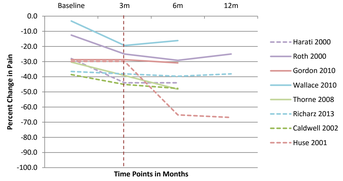
Figure 4.* Percent change in average, usual, or current pain scores over time among single-arm open-label trials: A - 6 to <12 months in duration;[23-28] B - ≥12 months in duration.[29-34,36-38]



* Some data points are shown as the nearest 3 monthly time point (i.e. 2 month point is shown at 3 months for Pappgallo and the 5 month point is shown at 6 months for Rauck).

- During the initial phase of opioid therapy in the RCTs and OL studies, a large decrease (often greater than 25%) in pain was reported; thereafter, analgesia was generally maintained through 6 and 12 months, with 5 studies[29,33,34,36,37] demonstrating maintenance of analgesia to 24 or 36 months.

Figure 5. Percent change in average, usual, or current pain scores over time among open-label extension studies.[56-63]



- Prior to the start of the OLE, the subjects in these studies were receiving opioid therapy.
- Percent change in pain was calculated from the baseline of the initial study, not the start of the OLE.
- In these OLE studies, pain was either maintained at a reduced level or was further reduced from start of the OLE to the end of the study.

Measures of Function (SF-36 or SF-12)

- Eleven studies included data on the physical component and on pain scores.[16,21,23,29,37,45,47,49,59,61,78]
- Nine studies included data on the mental component and on pain scores.[16,21,37,45,47,49,59,61,78]
- The data suggested a trend that as pain was reduced both physical and mental component scores improved.

CONCLUSIONS

- We performed a comprehensive review of data from 70 studies encompassing multiple designs (including RCTs, OL,OLE and epidemiology studies) and in varied populations (>19,000 patients; >16,000 patient years).
- These studies demonstrated reductions in pain that were maintained to the end of the study, which were at least six months and in some cases up to 3 years in duration – supporting the effectiveness of LOT for those patients who are able to tolerate opioids and remain treated over the long-term.
- Secondary endpoints of physical and mental functionality in 11 studies showed improved functionality which appeared to correlate with the relief of pain with LOT.
- Until newer, novel classes of effective analgesics are available with data to support their long-term effectiveness, opioids remain an option for patients with chronic pain severe enough to require daily, around-the-clock, long-term treatment and for which alternative treatment options are inadequate. Opioids remain one of the few options for patients suffering from moderate to severe chronic pain to alleviate pain. Efficacy considerations should be balanced by risks, including risks of addiction and overdose, when making prescribing decisions.
- This analysis did not account for variation in imputation methods used for assessing patient discontinuation which may impact the efficacy measures in these studies.

REFERENCES

References are available on the back of the poster handout or through this QR code.

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