Effectiveness of Polymer-Coated Extended-Release Morphine Sulfate Capsules in Older Patients with Persistent Moderate-to-Severe Pain: A Subgroup Analysis of a Large, Open-Label, Community-Based Trial

John Sasaki, MD1; Arnold J. Weil, MD2; Edgar L. Ross, MD3; and Bruce D. Nicholson, MD4

1Casa Colina Centers for Rehabilitation, Pomona, California; 2Non-Surgical Orthopedic & Spine Center, PC, Atlanta, Georgia; 3Pain Management Center, Brigham and Women’s Hospital, Boston, Massachusetts; and 4Division of Pain Medicine, Lehigh Valley Hospital & Health Network, Allentown, Pennsylvania

ABSTRACT

Background: Opioid analgesics may offer benefits over nonopioids in some older patients, especially those with moderate-to-severe pain. Polymer-coated extended-release morphine sulfate (P-ERMS) has been found to be efficacious and well tolerated in patients with chronic, moderate-to-severe, nonmalignant pain when used QD or BID.

Objective: The purpose of this analysis was to determine the effectiveness of P-ERMS in older patients (aged >65 years) with persistent, moderate-to-severe, inadequately controlled, nonmalignant pain.

Methods: This was a subgroup analysis of the older population from an open-label trial in community-based pain clinics in which patients underwent treatment with P-ERMS for persistent, moderate-to-severe, inadequately controlled, nonmalignant pain (≥4 on a scale of 0–10). Patients received P-ERMS at a dose determined by the investigator based on their previous analgesic regimen, QD (morning or evening) for a 4-week treatment period. Dose increases were permitted after weeks 1 and 2; switching to BID was allowed after week 2, if needed. Measurements included changes in pain and sleep scores (0–10 scale), quality of life (QOL) scores (physical and mental component summaries [PCS and MCS, respectively] of the 36-Item Short-Form Health Survey instrument), and patient and clinician assessments of current treatment based on a 9-point scale ranging from −4 to +4.

Results: One hundred forty-eight older patients (mean [SD] age, 73.4 [5.5] years) began treatment with P-ERMS; 86 (58.1%) of those patients completed the study. Pain and sleep scores significantly improved (decreased) from baseline to week 4 (7.4 vs 5.0 and 5.0 vs 3.2, respectively; both, P < 0.001). PCS and MCS scores significantly improved (increased) from baseline (27.7 vs 31.6 and 37.6 vs 40.8, respec-
CURRENT THERAPEUTIC RESEARCH

Results found in these older patients were similar to those observed in the younger patients (aged ≤65 years). A majority (71.4%) of the older patients remained on QD administration and took significantly lower mean daily doses than younger patients (77.0 vs 105.2 mg/d, respectively; P = 0.001). The dropout rate for the subgroup was 41.1%, which was similar to that reported in previous studies in mixed-age populations taking other extended-release morphine formulations. Of the patients who discontinued (n = 60), adverse events (AEs) were the most prevalent reason (n = 29). The most common treatment-related AEs were constipation (19.6%) and nausea (9.5%).

Conclusions: This subgroup analysis of a previously published study revealed that the older patients in that study who were receiving P-ERMS for persistent, moderate-to-severe, inadequately controlled, nonmalignant pain who completed the study attained significant improvements in pain, sleep, and QOL scores compared with baseline. Patient and clinician satisfaction with treatment increased significantly from baseline to study end. Older patients utilized significantly lower mean daily doses than younger patients (P < 0.001), and >70% remained on a QD administration regimen for the duration of the study.

Key words: analgesia, KADIAN, morphine, nonmalignant pain, persistent pain.

INTRODUCTION
Persistent pain, which continues for a prolonged period of time and may or may not be associated with a recognizable disease process, is common in the older population (aged ≥65 years). Approximately 25% to 60% of the community-dwelling older population and 45% to 80% of older nursing home residents have persistent pain,1-3 which is often suboptimally diagnosed and managed.3,4

American Geriatrics Society (AGS) guidelines1 for pain management recognize the usefulness of nonopioid and opioid analgesics in managing persistent pain. The recommended progression in most cases is from nonopioid analgesics such as acetaminophen to anti-inflammatory drugs, neurotransmitter-modulating and membrane-stabilizing drugs, and opioids.1 Acetaminophen is indicated for mild-to-moderate pain; however, it has a ceiling dose and must be used with caution in those patients with reduced renal or hepatic function.1 While traditional NSAID treatment might be beneficial in some patients, the risk for gastrointestinal bleeding is of concern.1 Cyclooxygenase-2 (COX-2) inhibitors are considered to offer a more tolerable gastrointestinal profile than nonselective COX inhibitors; however, studies have documented an increased risk for cardiovascular complications in patients receiving certain COX-2 inhibitors.5,6 The US Food and Drug Administration recommends COX-2 inhibitors only for selected patients who are not candidates for nonselective NSAIDs.7 They have also issued supplemental request letters to prescription NSAIDs sponsors, including celecoxib, to revise their labeling to include a
boxed warning highlighting the potential for increased risk for cardiovascular
events and gastrointestinal bleeding. Finally, certain adjuvant medications,
including certain antiepileptic drugs and duloxetine, have indications for neu-
ropathic pain and might be used alone or in combination with other anal-
gesics if the risk for side effects or drug–drug interactions is considered.

Opioid analgesics may benefit some older patients, especially those with
moderate-to-severe pain who have contraindications to long-term daily use of
NSAIDs. The potential effects of aging must be considered when prescribing opi-
oids. Reduced rates of systemic clearance and reduction in volume of distrib-
ution can yield increased initial plasma concentrations, while physiologic and
neurologic changes might increase the older patient's sensitivity to opioids.
Special precautions, including dose reduction, must be used in patients with
concurrent renal or hepatic disease, due to potential variations in drug clear-
ance and potential accumulation of active metabolites. While age-related
changes in drug disposition may lead to concern over adverse events (AEs),
they might also yield increased clinical response on lower doses of opioids.

AGS guidelines recommend long-acting or sustained-release opioids to
relieve continuous moderate-to-severe pain. Studies have examined the use of
opioids in older patients with cancer-related persistent pain. An English-
language literature search of MEDLINE (1996 to February 2007) and EMBASE
(1974 to February 2007) was conducted using the following key terms: pain,
analgesics-opioid, chronic or persistent pain, elder or old, aged, long-acting,
delayed-action, and controlled, time-, sustained-, prolonged- or extended-release.
The literature search revealed no specific studies on the use of extended-
release opioids in older patients with nonmalignant persistent pain. One ret-
rospective study of analgesics in an elderly nursing home population (n =
10,372) did indicate that the residents had attained benefits in functional sta-
tus (adjusted hazard ratio [AHR] = 1.85; 95% CI, 1.05–3.23) and social engage-
ment (AHR = 1.58; 95% CI, 0.99–2.50) while taking long-acting opioids. Challenges exist in study design and recruitment of older patients for clinical
trials.

Polymer-coated extended-release morphine sulfate* (P-ERMS) is a capsule
formulation of extended-release morphine sulfate indicated for the treatment
of moderate-to-severe chronic pain. Its pellets are a pH-dependent, polymer-
coated formulation that facilitates the release of morphine primarily in the alka-
line environment of the intestine, yielding effective plasma morphine concentra-
tions with a relatively small degree of fluctuation for up to 24 hours. The
bioavailability of P-ERMS is not affected by food. For these reasons, P-ERMS is
indicated for either QD or BID administration and can be administered without
regard to meals. The capsules can be administered orally, or can be opened so
the pellets contained in the capsules can be sprinkled on apple sauce or admin-
istered via gastric feeding tube.

The current analysis examined the effectiveness of P-ERMS in treating older patients, aged >65 years, who had unsatisfactory control of chronic, moderate-to-severe, nonmalignant pain with prior medication and participated in a previously published, large, open-label, community-based trial using P-ERMS. That trial found that P-ERMS is efficacious and well tolerated in patients with chronic, moderate-to-severe, nonmalignant pain when used QD or BID.

METHODS
Patients and Study Protocol

The KADIAN\textsuperscript{8}: Response Of Non-malignant, Under-treated Subjects with Moderate/Severe Pain (KRONUS-MSP) trial was a community-based, prospective, open-label trial involving patients attending 1 of 202 study sites throughout the United States. Participants were men and women aged ≥18 years who had persistent, moderate-to-severe, nonmalignant pain conditions for which treatment with an extended-release opioid was warranted. They were required to have had unsatisfactory response on their previous treatment regimen, as indicated by pain intensity of ≥4 on a scale of 0 (no pain) to 10 (worst pain imaginable). Patients with hypersensitivity to opioids, conditions that might contraindicate treatment with morphine, including gastrointestinal and respiratory conditions that might be worsened by opioid treatment, or who had a history of clinically significant laboratory abnormalities that might affect their safe participation in the study, were excluded.

The protocol, informed consent form, site regulatory package, and patient information were reviewed by IRB Company, Inc., Laguna Hills, California. The protocol was designed to ensure adherence to International Conference on Harmonisation Guidelines for Good Clinical Practice,\textsuperscript{27} Code of Federal Regulations Title 21, parts 50, 56, and 312 D,\textsuperscript{28} and the Declaration of Helsinki.\textsuperscript{29} No patient could enter the study until written informed consent was obtained either from the patient or from a legally appointed representative.

The study protocol was described in detail in a previous publication. Patients were randomized to receive P-ERMS in the morning (AM administration) or evening (PM administration). Investigators determined initial daily dose based on each patient's individual factors and pre-study analgesic regimen. Instructions to investigators included the suggestion that the starting dose of P-ERMS be reduced 50% from the equianalgesic dose of pre-study medication. After week 1, patients were queried for pain relief and rescue medication use, and the investigator could increase the dose if needed. After week 2, investigators could increase the dose for patients who had not yet increased their dose if needed; patients who had already increased their dose could be switched to a BID regimen. Immediate-release morphine was prescribed for breakthrough pain. No other opioids were allowed during the study period. Analgesics and other adjuvant medications such as acetaminophen, NSAIDs, corticosteroids, neuroleptics, anxiolytics, or antidepressants
were permitted only if the dose was anticipated to remain stable for the duration of the study.

The present study compared the results of patients aged >65 years with those of the remaining study population aged ≤65 years.

End Points

Effectiveness was assessed by determining the change from baseline to study end in pain, sleep interference, quality of life (QOL), and patient and clinician global assessments of treatment. Investigators were provided with standard question cards containing the visual numeric scale (VNS) to attain a uniformity of response.

Pain was assessed by a VNS score of 0 (no pain) to 10 (worst pain imaginable), based on the previous 24 hours. A 0 to 10 scale has been recognized as a good first-choice scale for measuring pain intensity in most older persons. Similarly, sleep was assessed by a VNS ranging from 0 (pain did not interfere with sleep at all) to 10 (pain completely interfered with sleep) during the previous 24 hours. Unlike the pain scale requirement of ≥4 points, there was no entry criterion for the sleep scale (ie, patients with no reported sleep problems were allowed to enter the trial).

QOL assessments were based on the 36-Item Short-Form Health Survey, version 2 (SF-36v2™; QualityMetric Inc., Lincoln, Rhode Island), a multipurpose survey yielding 2 main component scores (physical and mental), 8 subscale scores, and a health transition scale rating current health compared with health 1 year prior. Patients completed this form and sent it directly to the data analysis center in Orange, California.

Patients completed a global assessment of current treatment based on a 9-point scale ranging from -4 (completely dissatisfied; inadequately controlled pain, cannot function, disruptive administration schedule) to +4 (completely satisfied; pain controlled, convenient administration schedule, no side effects). Similarly, clinicians described their overall satisfaction with the treatment regimen by choosing a number ranging from -4 (completely dissatisfied; consider change to different drug or drug class) to +4 (completely satisfied; no change to drug dose or administration schedule, no side effects). Assessments were completed at baseline to describe satisfaction with the prior treatment regimen and after 4 weeks of P-ERMS treatment. Patients were then asked to complete an additional global assessment of treatment, if they were still receiving P-ERMS, 4 weeks following the completion of the study by means of a stamped, self-addressed business reply card.

Tolerability

AEs, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination or other means, were recorded on the case report form and assessed and summarized with regard to frequency, severity, and relationship to study medication.
Analyses

The safety population consisted of all patients who took ≥1 dose of P-ERMS; the modified intent-to-treat (mITT) population included all patients in the safety population who completed a valid baseline assessment and ≥1 post-baseline outcome assessment. Statistics after week 4 versus baseline were calculated on the mITT population using the paired t test, conducted against a 2-sided alternative hypothesis with a significance level of $P < 0.05$. One-way analysis of covariance, with baseline as the covariate for week 4 and the change from baseline at week 4, was used to compare results in older patients with those of patients aged ≤65 years, while a 2-sample t test was used to compare administration regimens between age groups. AEs were reported in the safety population. Statistical analyses were performed using SAS software, version 8.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Of the 1428 patients enrolled in the initial study, 1418 took ≥1 dose of study medication (safety population). There were 148 patients aged ≥66 years (mean [SD] age, 73.4 [5.5] years; median age, 73.0 years) who began the study. Five patients did not specify age. Of these, 71.5% were women and 89.8% were white. Among the younger patients (<65 years; n = 1265), 59% were women and 89.5% were white.

There were 146 older patients for whom disposition was recorded. Among the older patients, the most common medical conditions were back pain (12.8%), intervertebral disc degeneration not otherwise specified (NOS) (10.8%), spinal stenosis NOS (8.8%), localized osteoarthritis (8.1%), post-laminectomy syndrome (6.1%), and spondylosis (6.1%). Seventy-three (50.0%) of the older patients enrolled due to pain alone, 8 (5.5%) due to decreased QOL alone, and 65 (44.5%) due to pain and decreased QOL.

Eighty-six (58.9%) older patients completed the study, while 60 (41.1%) discontinued. Reasons for discontinuation were: AE, 29 (19.9%); patient’s decision, 23 (15.8%); lack of effectiveness, 3 (2.1%); noncompliance, 2 (1.4%); and missing/other, 3 (2.1%). Of the 103 older patients in the mITT population, 86 (83.5%) completed the study.

Older patients had statistically significant improvements in all outcomes after 4 weeks compared with baseline. The improvements in pain and sleep scores ($P < 0.001$) are shown in Figure 1.

Older patients recorded statistically significant increases in the QOL indices, including 7 of 8 SF-36v2 subscales (Figure 2). A significant improvement was also observed in health transition, the 1 scale for which a lower score indicates improvement (mean [SD], 3.5 [1.0] vs 3.2 [1.1]; $P = 0.004$). Mean (SD) physical component summary (PCS) scores increased significantly from baseline to week 4 (27.7 [6.9] vs 31.6 [6.7]; $P < 0.001$); mean (SD) mental component summary scores also increased from baseline (37.6 [12.2] vs 40.8 [12.0]; $P = 0.011$).
As in the original study population, the change in PCS scores in the subgroup also reached clinical relevance.26

Older patients and their clinicians expressed improved satisfaction with pain treatment after 4 weeks, as measured by the global assessment scores shown in Figure 3. Mean patient assessment scores improved from −1.2 at baseline to +1.1 at 4 weeks (P < 0.001). Mean clinician assessment scores improved from −1.5 at baseline to +1.4 at 4 weeks (P < 0.001).

Of the 86 older patients who completed the study on P-ERMS, 63 (73.3%) returned the business reply card 4 weeks later. Of these patients, 38 (60.3%) remained on P-ERMS after the study and 25 (39.7%) were not taking P-ERMS.

The improvements in pain and sleep, QOL, and patient and clinician global assessment scores were comparable to those seen in patients <65 years.

Older patients had significantly lower initial and final doses than younger patients (initial, P < 0.001; final, P = 0.001). The mean (SD) initial dose for older patients was 40.5 (34.1) mg/d (median, 20.0 mg). At the last administration adjustment following week 2, the mean (SD) dose was 77.0 (76.9) mg/d (median, 55.0 mg). Patients aged <65 years used a mean (SD) daily initial dose of 59.6 (54.3) mg (median, 50.0 mg) and a mean (SD) daily dose, after final adjustment, of 105.2 (97.8) mg (median, 80.0 mg).
Figure 2. Mean scores from the 36-Item Short-Form Health Survey, version 2 (scale 0–100) reported at baseline and 4 weeks by older patients with persistent moderate-to-severe pain receiving polymer-coated extended-release morphine sulfate capsules. PCS = Physical Component Summary; MCS = Mental Component Summary. *P < 0.001 versus baseline; †P < 0.05 versus baseline; §Based on the number of respondents to each question; ‡P < 0.01 versus baseline.
Figure 3. Patient and clinician global assessment scores. *P < 0.001 versus baseline; †Based on the number of respondents to each question; ‡Patients receiving polymer-coated extended-release morphine sulfate who provided a patient global assessment score on the business reply card.
A majority (71.4%) of the older patients remained on QD administration throughout the study. This proportion was significantly higher than that of the younger patients (55.6%; \( P = 0.004 \)). The remaining patients were on BID administration. After the final dose adjustment, the mean (SD) total daily dose was lower in older patients receiving P-ERMS QD compared with those receiving it BID (58.5 [48.8] mg vs 127.3 [110.5] mg, respectively).

Treatment-related AEs affecting >5% of the older population were constipation (29 [19.6%] patients), nausea (14 [9.5%]), dizziness (11 [7.4%]), sedation (10 [6.8%]), and somnolence (9 [6.1%]). There was no significant difference in the overall rate of AEs in patients who ended the study on QD administration versus those receiving BID administration (41.5% vs 38.5%); there were also no significant differences in the rate of individual AEs. Sixty (41.1%) patients discontinued the study. Twenty-nine (48.3%) discontinued the study due to an AE. The most common AEs causing discontinuation were constipation (11 [18.3%] patients) and nausea (7 [11.7%]). Other reasons for discontinuation were patient decision (23 [38.3%] patients), lack of effectiveness (3 [5.0%]), noncompliance (2 [3.3%]), and other (3 [5.0%]). There were 3 serious treatment-related AEs observed (nausea, vomiting, and dehydration) in 1 patient who was aged 75 years. This patient completely recovered and was discontinued from the study. There were no deaths among the older patients during study participation.

**DISCUSSION**

Results of this subgroup analysis suggest that older patients with persistent, moderate-to-severe, nonmalignant pain experienced significant decreases in pain and sleep interference, and increases in QOL were similar in comparison with younger subjects. Patients and clinicians reported increased satisfaction with P-ERMS compared with previous treatments. Of patients who completed the business reply card, 60% indicated that they remained on P-ERMS 4 weeks after study completion with continued improvement in satisfaction. Because responses on the business reply card were limited to those from patients who had completed the full study and had chosen to respond, they do not represent the full patient population.

Over 70% of older patients in the study remained on QD administration for the duration of treatment. This might have been associated with the reduced volume of distribution and rate of morphine clearance in older patients,\(^\text{14,15}\) and is consistent with reports that increased age is associated with a longer duration of pain relief on opioids.\(^\text{3,14}\) Alternately, it might be due to other factors affecting the pharmacodynamics of morphine\(^\text{14}\) or due to characteristics of the pain experience or goals of treatment in older patients.

The ability to dose with P-ERMS QD in most cases, and BID in the remaining cases, may be especially beneficial in older patients. AGS guidelines suggest that drug regimens be simplified as much as possible.\(^\text{1}\) The QD or BID administration schedule of P-ERMS, combined with the fact that it can be administered
without regard to meals,\textsuperscript{25} provides simplification to both patients and caregivers, whether in the community or in residential facilities. Studies have demonstrated increased compliance when a regimen requires QD versus TID and QID administration, and BID versus QID.\textsuperscript{31} Because the contents of the P-ERMS capsule can be sprinkled onto apple sauce or administered through a gastric feeding tube, patients might maintain the same medication regimen even if, as they age, they have difficulty swallowing whole capsules.

Older patients in the study experienced typical opioid-related AEs. Constipation, the most frequent AE, was reported in 19.6\% of older patients. Other studies of extended-release opioids in patients with a wide age distribution have demonstrated constipation rates of 27\% to 45\%;\textsuperscript{32,33} AGS guidelines recommend a prophylactic bowel regimen and management plan when long-term opioid treatment is initiated.\textsuperscript{1} The percentage of patients (29/148 [19.6\%]) who withdrew from the trial due to an AE was comparable to other studies of extended-release opioids for chronic pain.\textsuperscript{32,33}

The mean daily dose of P-ERMS was higher in older patients who dosed BID than in those who dosed QD. Yet, tolerability remained similar between the administration regimens. It is possible that the BID administration option served as a means of increasing the dose of P-ERMS for those who needed it to attain effectiveness without increasing the overall frequency of AEs.

Due to the challenges of performing research in older populations,\textsuperscript{22} few studies on opioids have been performed in patients aged >65 years. The KRONUS-MSP trial was not designed specifically to assess pain in older patients; however, the large sample size enabled identification and analysis of 148 older patients. While many patients demonstrated successful treatment outcomes, future prospective placebo-controlled studies should include outcome scales that have been validated in older patients, and should also address common concerns in older populations, such as cognitive function, ambulation, concomitant health issues, and cost. A study of longer duration would also be valuable to assess long-term effectiveness and safety.

While patients experienced statistically significant pain reductions from baseline (pain level 7.4), the mean pain level at study completion was still 5.0. It is possible that continuation of the study period or adjustment of the comprehensive pain management program might have yielded additional pain reduction. However, it is not realistic to expect complete absence of pain for some persistent pain conditions.\textsuperscript{1} It has been demonstrated that a 2-point decrease in pain scores on a 0 to 10 scale, which is equivalent to approximately a 30\% decrease when entry criteria require a score ≥4, is clinically important to patients.\textsuperscript{34} Therefore, the mean decrease of 2.4 points observed in this analysis, especially in patients with higher pain scores who had been receiving previous opioid medications, is noteworthy.

Doses in the older patients were titrated from a mean (SD) daily starting dose of 40.5 (34.1) mg/d up to 77.0 (76.9) mg/d after 2 weeks. The significant increase in mean daily dose ($P < 0.001$) might be indicative that these older
patients were underdosed on their previous medications, as is often seen in the older population. However, because investigators were instructed to initiate on a reduced starting dose of P-ERMS, the increase in mean daily dose might also reflect a return to therapeutic levels.

Although patients were instructed to report their weekly use of rescue medication and to bring the medication with them to each clinic visit, information on rescue medication use was not consistently recorded across the 202 study sites. Therefore, it was not possible to analyze rescue medication usage and the total daily dose of morphine. Monitoring of concomitant medications was also limited. Given that the study period lasted 4 weeks, it is unlikely that significant changes in concomitant medications would have been prevalent, but the possibility of bias does exist.

While older patients had improvement in all outcomes with generally good tolerability, interpretation of the results is limited by the lack of a placebo arm. Inclusion of a placebo arm would have required patients to taper off current medication prior to receiving study medication, and would not have reflected clinical practice. The role of opioids is already recognized in managing chronic pain in older patients. Future studies comparing the efficacy, tolerability, and cost-benefit ratio of various formulations (active controls) might provide additional information within an appropriate clinical framework. The withdrawal rate in this patient group (41.1%) also can be considered to be a limitation in interpreting the effectiveness of P-ERMS in the older patient population. This withdrawal rate, however, was similar to that reported with 4-week studies in mixed-age populations taking other extended-release morphine formulations. Additional studies would be beneficial to assess the long-term use of P-ERMS and other opioids in the older population.

CONCLUSIONS
This subgroup analysis of a previously published study revealed that the older patients in that study who were receiving P-ERMS for persistent, moderate-to-severe, inadequately controlled, nonmalignant pain who completed the study attained significant improvements in pain, sleep, and QOL scores compared with baseline. Patient and clinician satisfaction with treatment increased significantly from baseline to study end. Older patients utilized significantly lower mean daily doses than younger patients, and >70% remained on a QD administration regimen for the duration of the study.

ACKNOWLEDGMENTS
Publication support for this manuscript was provided by Alpharma Pharmaceuticals LLC, Piscataway, New Jersey. Writing and editorial support for this manuscript was provided by Medical Action Communications, Parsippany, New Jersey.
REFERENCES


**Address correspondence to:** John Sasaki, MD, Casa Colina Centers for Rehabilitation, 255 East Bonita Avenue, Pomona, CA 91767. E-mail: johnsasakimd@mac.com