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Evaluating the stability of opioid efficacy over 12 months in patients with chronic noncancer pain who initially demonstrate benefit from extended release oxycodone or hydrocodone: harmonization of Food and Drug Administration patient-level drug safety study data

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Abstract:
Opioids relieve acute pain, but there is little evidence to support the stability of the benefit over long-term treatment of chronic noncancer pain. Previous systematic reviews consider only group level published data which did not provide adequate detail. Our goal was to use patient-level data to explore the stability of pain, opioid dose, and either physical function or pain interference in patients treated for 12 months with abuse deterrent formulations of oxycodone and hydrocodone. All available studies in the Food and Drug Administration Document Archiving, Reporting, and Regulatory Tracking System were included. Patient-level demographics, baseline data, exposure, and outcomes were harmonized. Individual patient slopes were calculated from a linear model of pain, physical function, and pain interference to determine response over time. Opioid dose was summarized by change between baseline and the final month of observation. Patients with stable or less pain, stable or lower opioid dose, and stable or better physical function (where available) met our prespecified criteria for maintaining long-term benefit from chronic opioids. Of the complete data set of 3192 patients, 1422 (44.5%) maintained their pain level and opioid dose. In a secondary analysis of 985 patients with a measured physical function, 338 (34.3%) maintained their physical function in addition to pain and opioid dose. Of 2040 patients with pain interference measured, 788 (38.6%) met criteria in addition. In a carefully controlled environment, about one-third of patients successfully titrated on opioids to treat chronic noncancer pain demonstrated continued benefit for up to 12 months.

Keywords: Chronic noncancer pain, Back pain, Osteoarthritis, Treatment, 12-month studies, Opioid, Individual patient data, FDA, Meta-analysis

1. Introduction

The treatment of pain is an important focus of modern medical science, and opioids have played an important role in reducing human pain and suffering. Opioids have an extensively demonstrated efficacy in treating acute pain[8,23] and short-term benefits in treating chronic pain.[2,9] Originally developed to provide more humane treatment of patients with cancer pain, the use of extended release opioids in noncancer chronic pain has grown since the 1980s contributing to the wider availability of opioids. Research has also provided a better understanding of the addictive properties of opioids and the contribution of over prescribing to the opioid use disorder epidemic. Although the evidence for the personal and societal risks of opioids has rapidly expanded, there remain at least some patients who continue to report long-term pain and functional benefits from their use of opioid; however, there is little information to help guide the

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appropriate use. A recent meta-analysis of the available published data[10] reports a lack of high-quality published evidence on the long-term use of opioids based in part on inadequate details provided in the publications to judge the quality of the studies.

The absence of evidence for potential benefits and growing evidence for the potential harm has created concern that chronic opioid therapy may not be appropriate for any patients. Animal studies demonstrate the development of tolerance to opioid effects and opioid-induced hyperalgesia. Evidence for the adaptation of humans to opioid side effects and the need for higher doses in some pain phenotypes[16,31] have been used to suggest that opioid tolerance may also limit chronic benefit in patients. A growing number of observational database studies have demonstrated the potential risk of opioid misuse and abuse behavior in a subset of patients with pain syndromes using chronic opioid therapy.[14,20] However, the lack of accurate measures of the level of pain or other functional outcomes in these observational data make it difficult to study any potential benefits of opioids in the same data. As such, there is a need for a careful examination of prospectively collected outcomes on long-term opioid use in patients with chronic pain.

Although long-term randomized trials would be ideal to control for confounding and bias, they would be costly and ethically problematic. However, prospective observational 12 months safety studies were conducted as part of the approval process for abuse deterrent extended release (ER) opioids submitted to the Food and Drug Administration (FDA). No patient-level investigations of these data have been conducted to date. Although results from most of these studies were published, a systematic review in 2020 of the published data from 15 studies[4] included only 3 of the studies available through the FDA database. In addition, all systematic reviews presented only group mean data, and the lack of published protocol details often led to concerns about potential bias.[4,18,26] Access to the original protocols and careful reanalysis of patient-level responses can overcome a number of these concerns. The available data on patient's symptoms, opioid use, adverse events, and reasons for dropouts for all enrolled patients in FDA-mandated safety trials provide information on whether long-term chronic opioids may continue to have stable benefit for at least some patients. Understanding if some patients may continue to benefit from long-term therapy without increased doses or significant side effects is an important part of considering the potential for use of long-term opioid therapy, while reducing the inappropriate use of opioids, and not losing sight of our responsibility to reduce the burden of pain in our population.[6,24]

2. Methods

After establishing a contract with the FDA and obtaining IRB approval, we accessed the FDA Document Archiving, Reporting, and Regulatory Tracking System data management system. In addition to providing access to the data, the FDA reviewed this article to prevent disclosure of confidential data and provided editorial suggestions for clarity but had no role in our conclusions or our decision to publish.

To the best of our knowledge, the FDA files are the only available prospectively collected 12-month patient-level data of the chronic use of ER abuse resistant opioids. Twelve-month safety studies for ER oxycodone (5 studies) and ER hydrocodone (3 studies) were available in electronic Clinical Data Interchange Standards Consortium (CDISC) - Study Data Tabulation Model (SDTM) data format. Earlier studies of morphine and hydromorphone would have required extensive data entry and were not included.[4,18,26] The harmonization and analysis were conducted using R and STATA-SE Version-16 on FDA provided and encrypted computers.

Our primary goal was to determine the proportion of patients who demonstrated a combination of stable or reduced level of pain and stable or reduced opioid dose over the 12-month treatment period who had been enrolled after initially achieving pain control with titration to an effective study opioid dose. In studies which collected the data, we also analyzed the change over time in physical function using the SF36-Physical Function (PF-10) Scale[32] and pain interference from the Brief Pain Inventory Interference score (BPI-I)[21] available only in 2 and 5 studies, respectively. Similar to our analysis of pain, these were each examined separately, in combination with opioid dose. Each was also combined with the pain level and opioid dose criteria to determine the success rate for three critieria together. (see Venn Diagram—Supplemental Fig. 1, available at http://links.lww.com/PAIN/B380).

2.1. Sample of patients

Our study was limited to the patients reported to the FDA in the NDA submissions. The number of patients available at each study step is presented in a CONSORT diagram (**Fig. 1**). Our analysis was limited to data on patients who met inclusion and not exclusion criteria, signed consent, and entered the titration phase, as only 3 studies collected even limited data on patients screened. The primary criterion for the selection of patients to be enrolled was the clinician's judgement. Enrollment required the presence of chronic pain, current use of opioid (or opioid naïve and eligibility for a trial of opioids), and the absence of comorbidities that would limit participation or put patients at potential risk, including a history of or active opioid or alcohol abuse. After signing consent, patients in 4 studies were required to provide a urine drug screen with results appropriate to their current treatment regimen at the start of the study. Measures of risk for opioid misuse (COMM and SOAP) were only used in 2 studies and not analyzed.

The inclusion and exclusion criteria were generally consistent across all studies with small variations as indicated in Supplemental Table 1 (available at http://links.lww.com/PAIN/B380). All studies excluded patients with significant cardiac, renal, liver, gastrointestinal, pulmonary, metabolic, or nervous system disease that in the judgement of the clinician might put patients at risk during a 12-month study. All patients were asked to self-report comorbid conditions collected by a research coordinator or study investigator during the intake interview. Patients with complex etiologies of chronic low back pain (CLBP) or joint pain, such as underlying immune diseases, recent significant trauma, or major surgeries <6 months before enrollment, were also explicitly excluded. Significant uncontrolled psychiatric disease patients were also excluded, mostly based on clinician judgement, but 1 study used a HADs score of >12 for exclusion. As for body mass index, 2 studies required patients to be <45 kg/m^2 but the rest did not specify a criterion. Patients with treatable diseases such as hypertension, diabetes, depression, and anxiety were allowed in the study, provided they had a stable treatment regimen and appropriate ongoing medical care. Pain was measured on the 0-10 Numeric Rating Scale (0-10 NRS).

All enrolled patients underwent a dose titration period to determine the required level of opioid study drug, except for the 2 oxycodone studies focused on opioid-induced constipations. All patients previously on opioids enrolling in the pain studies were partially or fully withdrawn from their prestudy opioid until they reached an average pain $>4/10$.

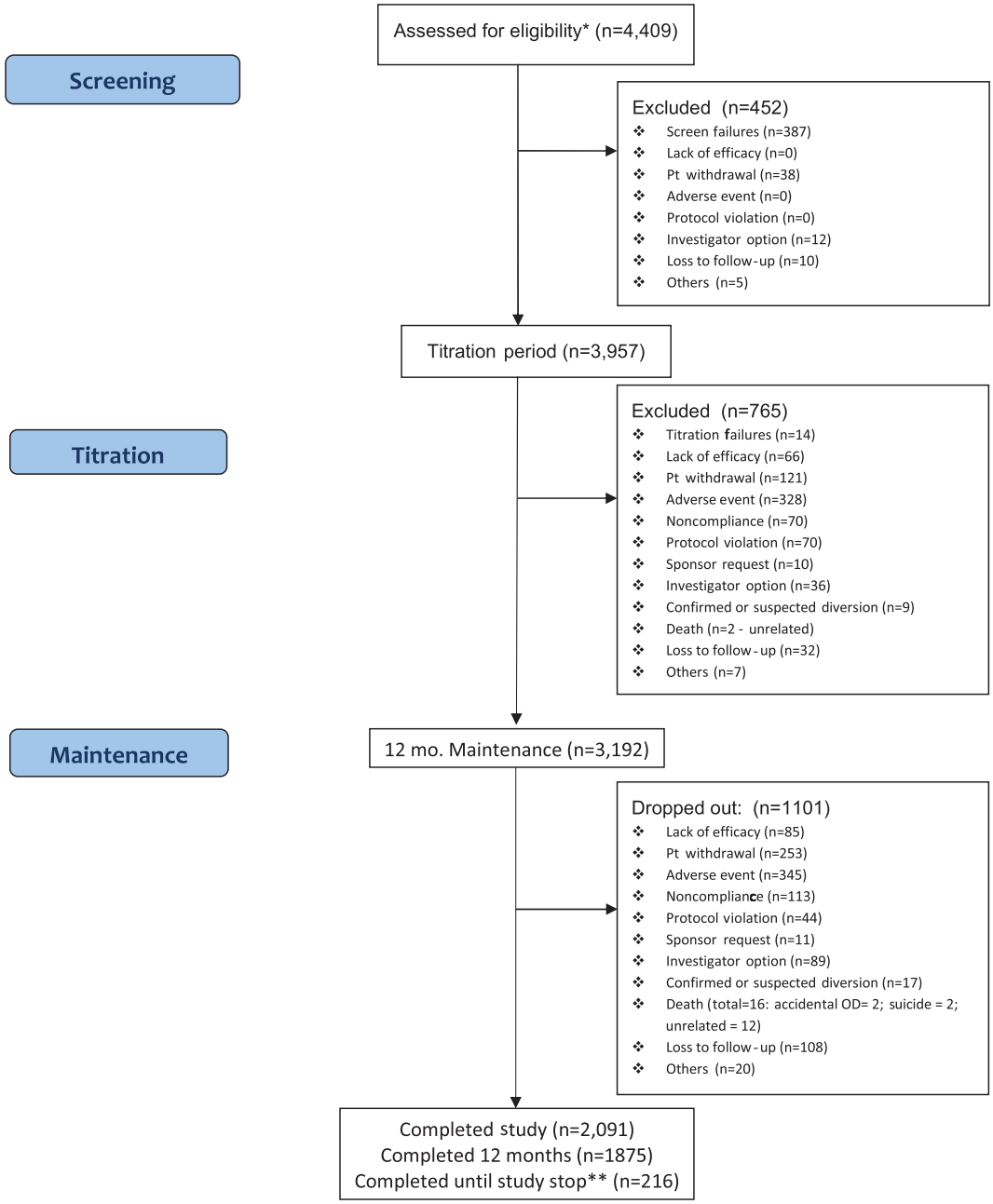

Figure 1. CONSORT diagram. *Only 3 studies provided numbers for screening patients. The remainder were either role overs from randomized trials or designated as "investigator judgement" in selection of patients to consent for titration. **Some studies stopped with patients still in process once number required had achieved 12 months of data.

Those who were opioid naïve but felt to be appropriate for opioid therapy were required to have pain >4/10 for enrollment. Both groups were then titrated to an effective study medication dose within study parameter dose ranges until they achieved a pain >4/10 in all cases or at least a 2-point drop to qualify for the maintenance phase. Once enrolled, patients were followed with at least monthly clinic visits to report pain levels and study drug use as well as to receive their next month supply of opioid medications. Patients who drop out were requested to complete a final pain rating and opioid use evaluation.

2.2. Harmonization

The primary issues in harmonizing and analyzing the different studies were as follows: (1) variable initial opioid titration periods and

methods; (2) variable scheduled times for the collection of data (pain scores, opioid use, etc.); (3) identifying a method for combining the change in pain, physical function, and BPI interference (BPI-I) with the change in opioid dose over time; and (4) variable rules about the use of rescue medication. These issues were dealt with as follows:

(1) The maximum time allowed for formal titration of patients onto a stable dose ranged from no separate titration up to 45 days. To normalize the data across all studies, we designated the first 45 days from initial dose of study medication as the titration period. Patients unable to achieve a stable dose, adequate pain control, or who chose to discontinue were reported as titration failures.
(2) Variable timing and frequency in data collection: to use all available pain data, conservatively deal with occasional missing data, and compensate for the normal variations over time, we calculated a linear fit of all the pain scores between baseline (end of titration period) and the end of the long-term study. We used the slope of the line to categorize patients as worse, stable, or better. Pain and BPI-I scores were categorized by designating changes in pain over 12 months on the 0-10 NRS of $>+1/10$ as worse, $+1/10$ to $-1/10$ as stable, and $<-1/10$ as better. PF-10 slope was calculated using the normalized standard SF-36 scale.[30] For opioid dose, we examined the change from baseline (end of titration) to the final 30-day period. A substantial number of patients had zero dose change, so zero was designated as stable, increase as worse, and decrease as better.
(3) Because the primary outcome considers both pain and opioid use, we used a combined analgesic outcome adapted from a 3 by 3 matrix analysis published by Burris et al.[7] Patients with stable or lower pain and stable or reduced opioid use were considered to have met our criteria for success, and all the other patients did not. The same method was used to combine physical function (PF-10) and BPI-I with dose. A stable or improved PF-10 and stable or improved BPI-I were each combined separately with the pain and dose combination for a more stringent analysis.
(4) Rules about the type and use of rescue medication varied broadly among studies with only 2 hydrocodone studies prespecifying and providing hydrocodone 5 mg/325 APAP as rescue. Two oxycodone and 1 hydrocodone study allowed use of the investigator designated prestudy rescue and did not record the amounts used. The 3 remaining oxycodone studies allowed only acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), again without recording amounts. Therefore, we could not include rescue in our calculation of chronic opioid use for our primary analysis. In the 2 studies that recorded rescue, we examined change in rescue use over the course of the study. Per protocol, if the patients consistently used more rescue, they were encouraged to titrate to a higher study drug dose, which was measured as part of our primary outcome.

Our primary analysis is a descriptive presentation of the number of patients who did or did not meet our criteria for success as described above. A 95% confidence interval (95% CI) is presented to show the precision of the estimates. The data were also stratified by several demographic factors of interest. In addition, we recorded the number and reasons for patients' discontinuation at each stage. We used all the available data and have been explicit about any choices made selecting the most reasonably conservative option to safeguard against overestimation of benefit or underestimation of risk. When appropriate and possible, sensitivity analyses were conducted to better understand how our choices might have affected results.

3. Result

All 8 of the 12-month safety studies available online in the FDA Document Archiving, Reporting, and Regulatory Tracking System were included, testing 6 ER abuse deterrent formulations (5 oxycodone—all published[3,5,15,28] and 3 hydrocodone—2 published[17,33]) conducted between 2005 and 2013. Only 2 oxycodone[28] and 1 hydrocodone[17] studies had been previously included in recently published meta-analyses.[4,18] The selection process for studies is outlined in the PRISMA Diagram (Supplemental Table 2, available at http://links.lww.com/PAIN/B380). All 3 hydrocodone and 3 of the 5 oxycodone studies were focused on the treatment of pain (Supplemental Table 2, available at http://links.lww.com/PAIN/B380). Two oxycodone with naloxone studies examined the relief of opioid-induced constipation. Patients were selected by the investigators based on inclusion and exclusion criteria (Supplemental Table 1, available at http://links.lww.com/PAIN/B380), focusing primarily on subjects with chronic low back pain (CLBP), osteoarthritis (OA), or other musculoskeletal pain either on opioids or designated as appropriate for opioid therapy by their referring physician. Three studies provided limited data on screened patients, which are included in our consort diagram. Most of the patient demographic data were collected in the titration period once consent was signed. Reasons for dropout were reported on 4409 patients. Of the 3957 who initiated the titration phase, 3192 (80.7%) were successfully titrated onto an effective dose of study medication and enrolled in the long-term study period. Reasons for patients dropping out from the study are detailed in the consort diagram (**Fig. 1**). Of note, 18 patients died during or shortly after study completion. Two were apparently accidental overdoses, 2 were intentional suicides, and the remaining 14 were unrelated (eg, myocardial infarction, renal disease, stroke, etc.).

3.1. Population of patients enrolled

The inclusion and exclusion criteria for each of the 8 studies restricted the population of patients enrolled to those on opioids (or if naïve, likely to benefit from opioids) and without significant histories of abuse. Specifically,

(1) 8 studies excluded those with current or past drug or alcohol abuse;
(2) 4 studies collected a prestudy urine drug screen and apparently excluded those with positive tests;
(3) 6 studies specified that investigators select "patients likely to benefit from opioids" without clear criteria;
(4) 7 studies specified investigators limit enrollment to patients likely to be compliant;
(5) 8 studies allowed prestudy opioid use; and
(6) 8 studies excluded patients with uncontrolled psychiatric disease and suicidality, with 7 based on clinician judgement and 1 based on a HADs score of >12.

Overall, the 8 studies had similar demographics (**Table 1**). In the population of 3192 patients enrolled in the long-term maintenance study, the overall mean age was 53.5 years (mean range 48-58 years), slightly more women (57.9%, mean range 49%-66%), predominately White (88.7%, mean range 78%-100%), and non-Hispanic (97.1%, mean range 90%-100%). In the pain-focused studies, the average body mass index was 31.3, and in the constipation studies, only weight was measured (average 82.8 kg). Of those enrolled, 2298 patients were designated opioid tolerant (daily use of opioids for $>$ 14-30 days before recruitment) and 894 as opioid naïve. By design, the primary pain syndromes treated in the pain-focused studies were

CLBP (77.4%) and/or OA (64.4%). The history of neuropathy was high (79.0%) in the hydrocodone studies most likely because of radicular symptoms in the patients with CLBP. Prestudy opioid use was predominately oxycodone (756/2298, 32.9%) and hydrocodone (869/2298, 37.8%). Although patients with severe active psychiatric comorbidities were excluded, 46.1%, 38.3%, and 43.8% of patients reported a history of comorbid depression, anxiety, and insomnia, respectively, at their baseline intake interview and 17.5% of the patients recruited into the pain-focused studies reported constipation. All trials except for 1 hydrocodone study allowed the continued use of nonopioid analgesics that were stable for 14 to 30 days before recruitment (**Table 1**). The use of NSAIDs was 48.1% and, for the adjuvant analgesics, was 21.8% for antiepileptics and 3.8% for duloxetine. The antidepressants (32.6%), antianxiety (29.7%), and hypnotics (15.5%) medication use was mostly in patients who reported consistent comorbidities, and 15.3% used concomitant benzodiazepines.

3.2. Titration period pain response

The average pain intensity score measured on the 0-10 NRS at the beginning of the titration period was 5.9/10 in the pain studies (**Table 2**). The constipation studies did not require patients to stop their medication, even temporarily. Patients who were successfully titrated (3192/3957, 80.7%) continued to the maintenance phase, with an average pain at the end of a 45-day titration of 3.9/10. As a sensitivity analysis of the effect of the length of the titration phase, we recalculated the outcome values using a 30-day and 60-day titration period which showed only small differences (**Table 3**). Therefore, we used the 45-day titration period which was the maximum used in any study.

The primary outcomes for the maintenance phase for up to 12 months included the categories of the change in pain, function (PF-10), pain interference (BPI-I), and opioid dose over time. Change in average pain over time varied in the patient population (**Fig. 2**), but 2144 of 3192 (67.1%) patients had improved or stable pain (**Table 2**). In the 2 hydrocodone studies which included a baseline and endpoint SF-36 (n = 985), the physical function subscale (PF-10) improved or was stable in 636 of 985 (64.5%) patients. Similarly, in the 5 studies with the BPI-I measured (n = 2042), 1341 of 2042 (65.7%) improved or were stable over time (**Table 2**). The change in opioid dose remained stable or was reduced for 2167 of 3192 (67.9%) patients out to 360 days (**Fig. 3** and **Table 2**). Slightly more patients increased than decreased their dose month by month (**Fig. 3**), but overall, 1025 of 3192 (32.1%) ended up on a larger dose (**Table 2**). Detailed reasons for dropouts during maintenance or titrations by the study type are presented in Supplemental Table 3 (available at http://links.lww.com/PAIN/B380) with the largest number for adverse events (673, 17.0%), patient decision to withdraw (374, 9.5%), lack of efficacy (151, 3.8%), and noncompliance or protocol violations (297, 7.5%).

For the primary outcome of those who achieved adequate benefit in the titration period and met criteria in the 12-month opioid ER studies, 1422 of 3192 (44.5%, 95% CI 45.5%-45.8%) patients had stable or lower pain and stable or decreased opioid use (**Table 2**). Of the remaining 1770 of 3192 (55.4%, 95% CI 52.0%-52.3%) patients, 664 of 3192 (20.8%) had increased pain with a decrease or stable opioid dose, 722 (22.6%) had an increase in their opioid dose with a decrease or stable pain, and 303 (9.5%) had an increase in both. Eighty one were missing a follow-up pain measure after titration and were treated as maintenance failures. When adding the requirement of a positive or stable PF-10 in the 985 patients who had this measure, 338 of 985 (34.3%, 95% CI 34.0%-34.5%) were improved or stable in all 3. Similarly adding the requirement of a better (ie, lower) or stable BPI-I in the 2042 who had this measure, 788 of 2042 (38.6%, 95% CI 38.5%-38.8%) were improved or stable in all 3 (**Table 2**). Including all the patients enrolled in both the titration and maintenance phases (n = 3957), 1422 of 3957 (35.9%) were improved or stable in pain and dose, whereas 2535 of 3957 (64.1%) got worse in at least one characteristic or were missing. Requiring the PF-10 function scale criteria, there were 338 of 1251 (27.0%). For patients with the BPI-I, the successful percentage drops to 788 of 2526 (31.2%).

There was a sizable difference in the percent of patients meeting criteria between the pain and constipation types of studies. For patients in pain studies during the maintenance phase, 1111 of 2738 (40.6%) met our criteria for pain and dose success, whereas in the constipation-focused studies, it was 311 of 454 (68.5%) (**Table 2**). There were only small differences when stratified by sex, prestudy opioid and opioid naïve categories, and titrated study opioid dose categories (**Table 3**). There was a potential trend in the rate of patients meeting our criteria for success with age which increased from 40.2% at age 18 to 49 years to 51.3% in those patients older than 60 years old.

The overall number of dropouts was 1866 of 3957 (47.2%) during both titration and maintenance phases and 1101 of 3192 (34.5%) in the maintenance phase alone (**Fig. 1**). The dropout categories of "lack of efficacy" and "patient withdrawal" which probably represent patients not getting adequate pain relief totaling 338 of 1101 (30.6%). Specific adverse effects accounted for 345 of 1101 (31.3%) of the dropouts. Of note, the overall dropout rate is much lower in the constipation studies 55 of 454 (12.1%) (Supplemental Table 3, available at http://links.lww.com/PAIN/B380). This difference is evident across all disposition categories.

4. Discussion

In the harmonized patient-level data of people with predominately musculoskeletal non–cancer-related chronic pain, we identified a group of patients (44.5% of those successfully titrated and 35.9% of those who entered titration) who maintained or reduced their pain score on a stable or smaller dose of ER opioid for up to 12 months. Also important is that 55.4% and 64.1% of the patients, respectively, did not meet this criterion. In a less conservative approach, if we consider only patient's report of pain (without considering dose), 67.6% of those with successful titration remained stable or improved, which drops to 54.3% if we include those dropping out during titration. In those for whom physical function (PF-10) was also measured (n = 985), the group who exhibited improvement or stability in all 3 measures was 34.3% and 27.0%, respectively. In those for whom pain interference (BPI-I) was also measured (n = 2042), improvement or stability in all 3 measures was 38.6% and 31.2%, respectively.

The existence of a sizeable group of patients with predominately CLBP and OA meeting our criteria for stable or improved status demonstrates that at least some patients, who demonstrate a clinically important efficacy from abuse deterrent ER opioid analgesics during a titration period, maintain stable efficacy demonstrated for pain relief, improved function, and reduced pain interference for up to 12 months in the treatment of chronic pain. The existence of a successful group demonstrates the potential benefit of chronic opioid therapy and supports the consideration of such therapy in a carefully selected and monitored chronic pain population who do not achieve adequate pain control with other approaches. It is also clear that even in a

Table 1

Patient demographics.

	Compound	Hydrocodone	Oxycodone	Average for pain studies	Oxycodone	Average for all studies
	Symptom	Pain	Pain		Constipation	
	Number	(n = 1427)	(n = 1311)	(n = 2738)	(n = 454)	(n = 3192)
Age	Mean (SD)	52.1 (11.8)	53.7 (11.8)	52.9 (11.8)	57.1 (10.8)	53.5 (11.8)
Sex	Female (%)	809 (56.7%)	752 (57.4%)	1561 (57.0%)	287 (63.2%)	1848 (57.9%)
Race	White (%)	1154 (80.9%)	1224 (93.4%)	2378 (86.9%)	453 (99.8%)	2831 (88.7%)
Ethnic	Hispanic (%)	78 (5.5%)	14 (1.1%)	92 (3.4%)	0 (0%)	92 (2.9%)
BMI (Kg/Msq)	Mean (SD)	31.7 (7.3)	30.3 (6.1)*	31.3 (6.8)		
Weight kg					82.8 (18.5)	
Previous opioid (%)	Opioid naïve	370 (25.9%)	524 (40.0%)	894 (32.7%)	0 (0%)	894 (28.0%)
	Opioid tolerant	1057 (74.1%)	787 (60.0%)	1844 (67.3%)	454 (100%)	2298 (72.0%)
Specific opioids (% tolerant)	Morphine	105 (9.9%)	31 (3.9%)	136 (7.4%)	33 (7.3%)	169 (7.4%)
	Oxycodone	286 (27.1%)	233 (29.6%)	519 (28.1%)	237 (52.2%)	756 (32.9%)
	Hydrocodone	756 (71.5%)	113 (14.4%)	869 (47.1%)	0 (0.0%)	869 (37.8%)
	Hydromorphone	19 (1.8%)	8 (1.0%)	27 (1.5%)	13 (2.9%)	40 (1.7%)
	Fentanyl	43 (4.1%)	14 (1.8%)	57 (3.1%)	24 (5.3%)	81 (3.5%)
	Tramadol/tapentadol	170 (16.1%)	241 (30.6%)	411 (22.3%)	93 (20.5%)	504 (21.9%)
	Others	39 (3.7%)	12 (1.5%)	51 (2.8%)	14 (3.1%)	65 (2.8%)
Pain by history†	Chronic low back	1348 (94.5%)	778 (59.3%)	2126 (77.6%)	345 (76.0%)	2471 (77.4%)
	Fibromyalgia	66 (4.6%)	20 (1.5%)	86 (3.1%)	29 (6.4%)	115 (3.6%)
	Headache/migraine	435 (30.5%)	312 (23.8%)	747 (27.3%)	46 (10.1%)	793 (24.8%)
	Osteoarthritis	1290 (90.4%)	463 (35.3%)	1753 (64.0%)	302 (66.5%)	2055 (64.4%)
	Neuropathy	1127 (79.0%)	243 (18.5%)	1370 (50.0%)	243 (53.5%)	1613 (50.5%)
Comorbidities by history	Anxiety	636 (44.6%)	458 (34.9%)	1094 (40.0%)	127 (28.0%)	1221 (38.3%)
	Constipation	299 (21.0%)	181 (13.8%)	480 (17.5%)	454 (100.0%)	930 (29.1%)
	Depression	748 (52.4%)	536 (40.9%)	1284 (46.9%)	189 (41.6%)	1473 (46.1%)
	Diabetes - type 2	264 (18.5%)	198 (15.1%)	462 (16.9%)	54 (11.9%)	516 (16.2%)
	Gastro-esophogeal Reflux	466 (32.7%)	315 (24.0%)	781 (28.5%)	31 (6.8%)	812 (25.4%)
	Hypertension	733 (51.4%)	541 (41.3%)	1274 (46.5%)	203 (44.7%)	1477 (46.3%)
	Obesity	232 (16.3%)	94 (7.2%)	326 (11.9%)	43 (9.5%)	369 (11.6%)
	Insomnia	724 (50.7%)	505 (38.5%)	1229 (44.9%)	169 (37.2%)	1398 (43.8%)
	Sleep apnea	114 (8.0%)	33 (2.5%)	147 (5.4%)	8 (1.8%)	155 (4.9%)
Concomitant medications by history‡	NSAIDS	694 (48.6%)	687 (52.4%)	1381 (50.5%)	154 (33.9%)	1535 (48.1%)
	Muscle relaxants§	395 (27.7%)	268 (20.5%)	663 (24.2%)	34 (7.5%)	697 (21.8%)
	Acetaminophen	984 (69.0%)	218 (16.6%)	1202 (43.9%)	95 (20.9%)	1297 (40.6%)
	Antianxiety	514 (36.0%)	292 (22.3%)	806 (29.4%)	143 (31.5%)	949 (29.7%)
	Benzodiazepines‖	305 (21.4%)	140 (10.7%)	445 (16.3%)	44 (9.7%)	489 (15.3%)
	Antidepressants	449 (31.5%)	392 (29.9%)	841 (30.7%)	199 (43.8%)	1040 (32.6%)
	Duloxetine¶	88 (6.2%)	18 (1.4%)	106 (3.9%)	15 (3.3%)	121 (3.8%)
	Antiepileptics	351 (24.6%)	213 (16.3%)	564 (20.6%)	132 (29.1%)	696 (21.8%)
	Antipsychotics	55 (3.9%)	41 (3.1%)	96 (3.5%)	30 (6.6%)	126 (3.9%)
	Hypnotics and sedatives	293 (20.5%)	153 (11.7%)	446 (16.3%)	48 (10.6%)	494 (15.5%)

* Only 2 of 3 oxycodone studies reported BMI.

† Percentages add up to greater than 100% because many patients reported more than one pain type.

‡ Some patients reported more than one previous drug.

§ Includes cyclobenzaprine, tizanadine, and carisoprodol.

‖ Benzodiazepines are a subset of the antianxiety category.

¶ Duloxetine is a subset of the antidepressant category.

carefully selected group of patients, a sizeable number of patients do not remain on a stable dose or maintain a stable level of symptoms over the same period indicating the importance of careful monitoring during treatment.

To interpret these findings in the context of the growing concerns about the use of long-term opioids, we must consider what else is known about the treatment of pain. Substantial evidence has been generated[25] that patients with acute or chronic pain should be approached from a multidisciplinary perspective starting with multimodal nonopioid therapeutic approaches, often including nonsteroidal anti-inflammatories. Studies have demonstrated that NSAIDs can be as effective as opioids for the treatment of conditions such as CLBP and OA[22] in a population of patients without serious contraindications to NSAID use. However, another interpretation of such equivalency studies is that opioids work as well as NSAIDs. The article by Krebs[22] reported a clinically important (ie, ≥30% change in pain) improvement in pain in 54% of the NSAID tolerant nonopioid group, leaving 46% of the patients reporting inadequate pain relief. Although it remains unclear how to best treat patients who cannot take or who do not get adequate relief from NSAIDs,[13,19,29] a trial of opioids remain a viable option for some. In such patients, our data also support the need for careful monitoring because a significant number

Table 2

Outcomes.

Compound	Hydrocodone	Oxycodone	Average for pain studies	Oxycodone	Average for all studies
Symptom	Pain	Pain		Constipation*	
Number	(n = 1427)	(n = 1311)	(n = 2738)	(n = 454)	(n = 3192)
Mean pain intensity (0-10) NRS					
Study enrollment	6.25 (1.66)	5.59 (2.04)	5.93 (1.88)	3.42 (1.55)	5.58 (2.04)
Posttitration	3.45 (1.78)	4.45 (2.03)	3.93 (1.97)	3.47 (1.75)	3.86 (1.94)
Study 12 mo. Final	4.00 (2.07)	4.04 (2.13)	4.02 (2.10)	3.53 (1.92)	3.95 (2.08)
Mean opioid doses (MEQ†)					
At enrollment	51.8 (61.9)	68.2 (39.7)	54.9 (58.7)	NA (NA)	54.9 (58.7)
Posttitration baseline	61.8 (36.5)	72.7 (50.6)	67.0 (44.2)	83.0 (40.3)	69.3 (44.0)
Study 12 mo. Final	66.1 (39.4)	94.3 (68.3)	79.6 (56.9)	59.4 (33.3)	76.7 (54.7)
Outcome—patients meeting criteria N (%)					
For dose	(n = 1427)	(n = 1311)	(n = 2738)	(n = 454)	(n = 3192)
Better	136 (9.5%)	195 (14.9%)	331 (12.1%)	285 (62.8%)	616 (19.3%)
Same	882 (61.8%)	549 (41.9%)	1431 (52.3%)	120 (26.4%)	1551 (48.6%)
Worse	409 (28.7%)	567 (43.2%)	976 (35.6%)	49 (10.8%)	1025 (32.1%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
For pain	(n = 1427)	(n = 1311)	(n = 2738)	(n = 454)	(n = 3192)
Better	288 (20.2%)	492 (37.5%)	780 (28.5%)	101 (22.2%)	881 (27.6%)
Same	563 (39.5%)	453 (34.6%)	1016 (37.1%)	247 (54.4%)	1263 (39.6%)
Worse	547 (38.3%)	316 (24.1%)	863 (31.5%)	104 (22.9%)	967 (30.3%)
Missing	29 (2.0%)	50 (3.8%)	79 (2.9%)	2 (0.4%)	81 (2.5%)
For PF-10‡	(n = 985)		(n = 985)		(n = 985)
Better	385 (39.1%)		385 (39.1%)		385 (39.1%)
Same	251 (25.5%)		251 (25.5%)		251 (25.5%)
Worse	318 (32.3%)		318 (32.3%)		318 (32.3%)
Missing	31 (3.1%)		31 (3.1%)		31 (3.1%)
For BPI-I§	(n = 1427)	(n = 364)	(n = 1791)	(n = 251)	(n = 2042)
Better	310 (21.7%)	53 (14.6%)	363 (20.3%)	127 (50.6%)	490 (24.0%)
Same	604 (42.3%)	199 (54.7%)	803 (44.8%)	48 (19.1%)	851 (41.7%)
Worse	468 (32.8%)	105 (28.8%)	573 (32.0%)	75 (29.9%)	648 (31.7%)
Missing	45 (3.2%)	7 (1.9%)	52 (2.9%)	1 (0.4%)	53 (2.6%)
For pain and dose	(n = 1427)	(n = 1311)	(n = 2738)	(n = 454)	(n = 3192)
Patients met criteria	593 (41.6%)	518 (39.5%)	1111 (40.6%)	311 (68.5%)	1422 (44.5%)
Patients did Not meet criteria or missing	834 (58.4%)	793 (60.5%)	1627 (59.4%)	143 (31.5%)	1770 (55.4%)
For PF-10‡ and dose	(n = 985)	(n = 0)	(n = 985)	(n = 0)	(n = 985)
Patients met criteria	514 (52.2%)	n/a	514 (52.2%)	n/a	514 (52.2%)
Patients did Not meet criteria or missing	471 (47.8%)	n/a	471 (47.8%)	n/a	471 (47.8%)
For BPI-I§ and dose	(n = 1427)	(n = 364)	(n = 1791)	(n = 251)	(n = 2042)
Patients met criteria	679 (47.6%)	230 (63.2%)	909 (50.8%)	141 (56.2%)	1050 (51.4%)
Patients did Not meet criteria or missing	748 (52.4%)	134 (36.8%)	882 (49.2%)	110 (43.8%)	992 (48.6%)
For pain, dose, and PF-10	(n = 985)	(n = 0)	(n = 985)	(n = 0)	(n = 985)
Patients met criteria	338 (34.3%)	n/a	338 (34.3%)	n/a	338 (34.3%)
Patients did Not meet criteria or missing	647 (65.7%)	n/a	647 (65.7%)	n/a	647 (65.7%)
For pain, dose, and BPI-I	(n = 1427)	(n = 364)	(n = 1791)	(n = 251)	(n = 2042)
Patients met criteria	469 (32.9%)	194 (53.3%)	663 (37.0%)	125 (50.2%)	788 (59.3%)
Patients did Not meet criteria or missing	958 (67.2%)	170 (46.7%)	1128 (62.9%)	126 (50.2%)	1254 (61.4%)

* The constipation trials did not have a withdrawal period.
† MEQ, morphine equivalent units.
‡ PF-10—10-item function scale from Short Form-36.
§ BPI-I—Brief Pain Inventory interference scale.

Table 3

Stratification of outcome by demographic categories.

Category	Total numbers	Patients met criteria	Patients did not meet criteria	Missing values
Sex				
Female	1848	812 (43.9%)	986 (53.4%)	50 (2.7%)
Male	1344	610 (45.4%)	703 (52.3%)	31 (2.3%)
Opioid category				
Opioid naïve—pain study	894	343 (38.4%)	529 (59.2%)	22 (2.5%)
Previous opioid—pain study	1844	768 (41.6%)	1019 (55.3%)	57 (3.1%)
Previous opioid—constipation	454	311 (68.5%)	141 (31.1%)	2 (0.4%)
Age category				
18–49 y.	1108	430 (38.8%)	634 (57.2%)	44 (4.0%)
50–59 y.	1095	491 (44.8%)	582 (53.2%)	22 (2.0%)
60 + yrs.	989	501 (50.7%)	473 (47.8%)	15 (1.5%)
Titrated opioid dose Category				
< 50 mg MEQ	1243	578 (46.5%)	635 (51.1%)	30 (2.4%)
50-89.9 mg MEQ	999	409 (40.9%)	569 (57.0%)	21 (2.1%)
≥ 90 mg MEQ	949	435 (45.8%)	485 (51.1%)	29 (3.1%)
Sensitivity analysis				
30 d titration	3399	1427 (42.0%)	1891 (55.6%)	81 (2.4%)
45 d titration	3192	1422 (44.5%)	1689 (52.9%)	81 (2.5%)
60 d titration	3047	1413 (46.4%)	1545 (50.7%)	89 (2.9%)

of such patients required increased doses or had increased pain over 12 months. In considering the degree of pain reported by the aging population in the United States and increased lifespans after cancer diagnoses, we must consider all possible therapeutic interventions which could include opioids for at least some.

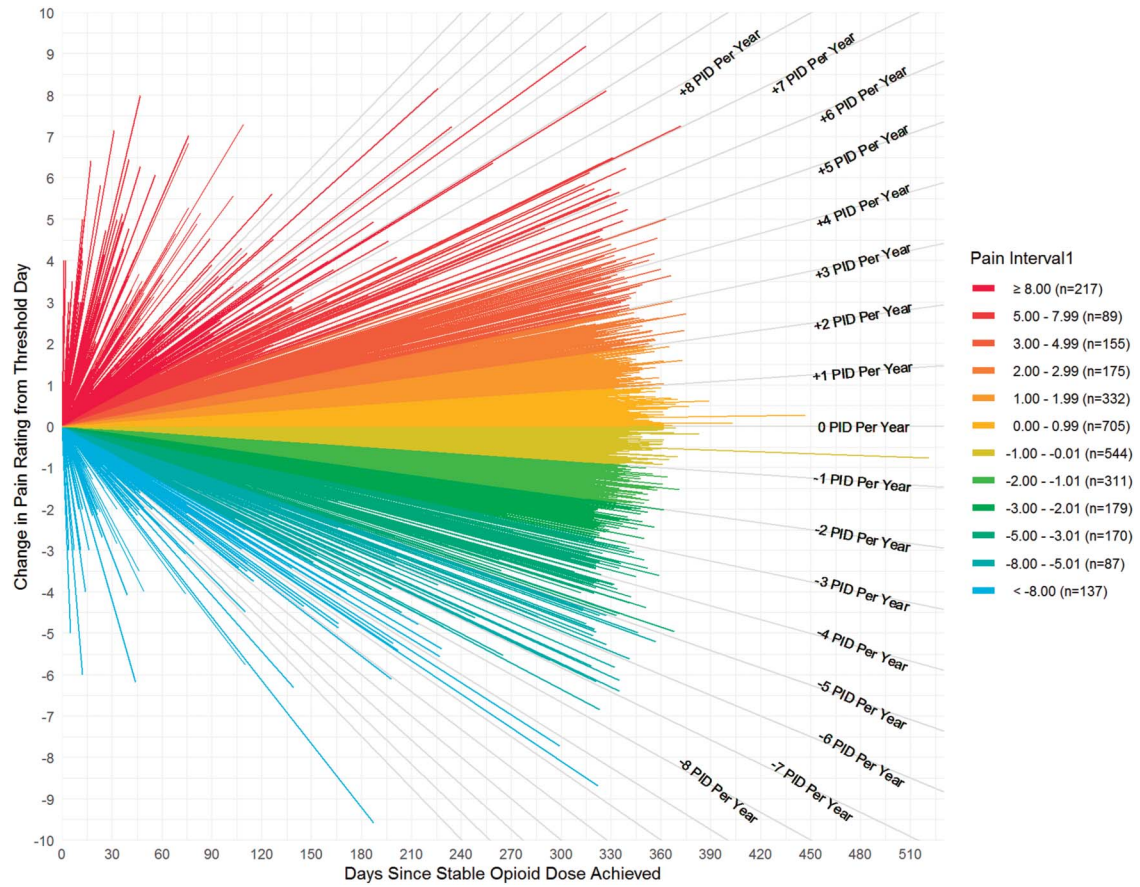

Figure 2. Individual patient-level linear model of the change in pain graphed by days for all patients (n = 3192). Positive values (orange to red) indicate patients whose pain increased and negative values (green to blue) those whose pain decreased. Pain values of between +1 and −1 considered stable (light orange and light green). For patients who dropped out, end of the line represents the time point when they dropped out. Gray line labels indicate changes in pain intensity differences estimated from the value of the linear models of patient data interpreted over length of study or to the point of drop out.

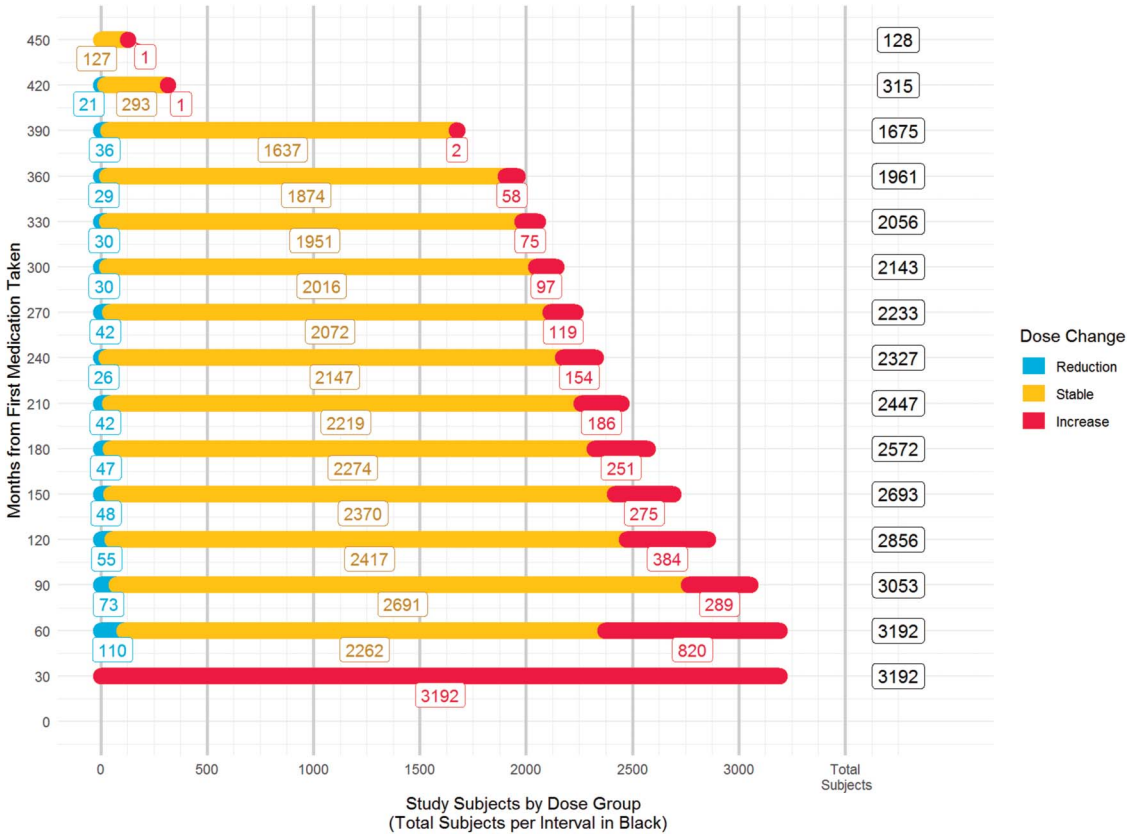

Figure 3. Number of patients enrolled with net dose changes by 30-day periods from first drug exposure to the end of study. The yellow bar represents patients whose opioid dose remained in that 30 days, blue those who used a lower dose, and red those who used a higher dose. The number of patients changing dose each month varied somewhat by study consistent with restrictions in the timing of additional changes in drug allowed but was small overall. As expected, a large number of patients changed dose over the first 2 months during the titration period and a much smaller number in later months. All data are shown. Values above 360 days reflect study data collected in some patients whose final visits extended beyond the stop date at 360 days.

There are important limitations to consider. First, without a control group in these observational studies, we cannot be certain what might have happened if an equivalent group of patients had been kept off of opioids for the same time period. Future studies should better assess all patients screened and the rescue medication used as well as could be designed to randomly withdraw patients from treatment in a blinded fashion multiple times over the course of 12 months to demonstrate ongoing efficacy; however, such studies have not been conducted. Selection bias is always a potential issue in observational studies.[11] By design, all studies of opioids enroll patients currently taking or willing to take opioids and who volunteer for a clinical study so may not represent the general population of chronic pain patients. Also, our data come from studies of long-acting abuse deterrent opioids and may not be directly applicable to other opioid forms; however, in the current clinical environment in the United States, the abuse deterrent formulations are becoming the primary form of long-acting opioids prescribed in clinical practice. Also, rescue medications were not considered in our analysis because of a broad variability of drugs used for rescue and inadequate capture of the data in some of the studies; however, patients who required substantial additional rescue were encouraged to move to the next level of the ER opioid therapy which was specifically recorded. In addition, the 2 studies that carefully measured the number of rescue pills taken each month, the use was 2 to 3 per day on average. Although there were some missing data, they were limited by the requirement that patients had to provide questionnaire responses to receive subsequent prescriptions of the study opioid and the prospective collection of the specific data elements.

As in all clinical studies, the population studied here may not reflect the full population of chronic pain patients. We include all know long-term studies of oxycodone ER and hydrocodone ER, except a registry study which was conducted independently from an FDA submission,[27] but not the other published opioid studies considered in the recent systematic review.[4] As such, our results are only directly applicable to these 2 products.[27] Our results are also consistent with the findings of one additional study comparing the use of the fentanyl patch to oral ER morphine in 680 opioid naïve patients with CLBP,[1] in which 553 patients completed the study with approximately 90% having stable or lower pain over the course of the 13-month study. This study did not examine the combined outcome of pain and dose.

The careful selection of patients included in the studies analyzed has been discussed above, so the applicability of our findings to a broader population must be considered in light of the study inclusion and exclusion criteria. In addition, the enrolled patients consisted of people willing to participate in a clinical trial who were determined to be eligible by their treating physician for chronic opioid therapy, and all patients were carefully monitored. In addition, patients with severe medical comorbidities, a known history of drug abuse disorder, or a severe psychiatric condition were excluded, so we cannot know if our results apply to such patients. However, these criteria are consistent with the patient characteristics that would be appropriate to consider before starting any patient on opioid therapy.

In considering our study in the light of other published data, reviews of earlier publications on the long-term use of opioids including both the NIH commissioned report[10] and 2 recent Cochrane guidelines[9,12] have reported little or no strong evidence for long-term use, noting the poor quality of the data provided in such publications.[4] Our study overcomes some of these concerns by analyzing individual patient responses rather than group data in more than 3000 study participants. We also had access to the full study protocols and study results, allowing us to provide substantially more information about all aspects of these eight different clinical trials.

In conclusion, our study presents evidence for existence of a group of patients who maintain stable pain and physical function (PF-10) or pain interference (BPI-I) while using stable doses of abuse deterrent ER oxycodone and hydrocodone for up to 12 months. The existence of a group of patients who demonstrate continued benefit does not imply that opioids should be considered as first line for chronic pain therapy nor does it answer the question of what might have happened to the same patients had they not been started on opioids in the first place. However, in situations where NSAIDs are contra-indicated, or they and other nonopioid approaches do not provide adequate pain reduction, a trial of opioids may be considered when used in an appropriately selected population with careful monitoring over time. Overall, the results of this study provide data that helps to inform the medical community on the potential for appropriate use of long-term opioids. Careful selection of patients and careful ongoing monitoring are needed to maximize their potential benefit and avoid their inappropriate use. The exact percentage of patients who could benefit from long-term opioid therapy in the general pain population cannot be estimated from our study; however, because the adequate control of pain remains a major challenge in the practice of medicine today, it is important that we consider all possible therapies to alleviate suffering and to do so with as much evidence as possible on the appropriate use of such therapies.

Conflict of interest statement

J.T. Farrar received research grants and contracts from the US Food and Drug Administration and National Institutes of Health as well as consulting fees from Analgesic Solutions, Aptinyx, Biogen, Opioid Postmarketing Consortium, Daiichi Sankyo, DepoMed, Evadera, Jansen, Lilly, Novartis, Vertex, and Pfizer; DSMB services from NIH-NIA; and Cara Therapeutics. W.B. Bilker served as a member of a DSMB for Genentech. C.E Argoff served as a consultant for Collegium Pharmaceuticals, Teva Pharmaceuticals, Pfizer, Kaleo, Daiichi Sankyo, and Astra Zeneca. J. Haythornthwaite serves as the Treasurer of the United States Association for the Study of Pain. N.P. Katz is an employee of WCG Analgesic Solutions, a clinical research services company with many clients in the pharmaceutical and medical device industry. I. Gilron received industry research support from Biogen, Eupraxia, Novaremed, and Teva. The remaining authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B380.

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References

[1] Allan L, Richarz U, Simpson K, Slappendel R. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. Spine 2005;30:2484–90.
[2] Argoff C, Arnstein P, Stanos S, Robinson CY, Galer BS, Gould E, Gammaitoni A. Relationship between change in pain intensity and functional outcomes in patients with chronic pain receiving twice daily extended-release hydrocodone bitartrate. J Opioid Manag 2015;11: 417–24.
[3] Arora S, Setnik B, Michael D, Hudson JD, Clemmer R, Meisner P, Pixton GC, Goli V, Sommerville KW. A multicenter, 12-month, open-label, single-arm safety study of oxycodone-hydrochloride/ naltrexone-hydrochloride extended-release capsules (ALO-02) in patients with moderate-to-severe chronic noncancer pain. J Opioid Manag 2014;10:423–36.
[4] Bialas P, Maier C, Klose P, Hauser W. Efficacy and harms of long-term opioid therapy in chronic non-cancer pain: systematic review and meta-analysis of open-label extension trials with a study duration >/=26 weeks. Eur J Pain 2020;24:265–78.
[5] Blagden M, Hafer J, Duerr H, Hopp M, Bosse B. Long-term evaluation of combined prolonged-release oxycodone and naloxone in patients with moderate-to-severe chronic pain: pooled analysis of extension phases of two Phase III trials. Neurogastroenterol Motil 2014;26:1792–801.
[6] Bonnie RJ, Schumacher MA, Clark JD, Kesselheim AS. Pain management and opioid regulation: continuing public health challenges. Am J Public Health 2019;109:31–4.
[7] Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15: 2403–13.
[8] Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, Mulla SM, Lopes LC, Vogel N, Chen E, Kirmayr K, De Oliveira K, Olivieri L, Kaushal A, Chaparro LE, Oyberman I, Agarwal A, Couban R, Tsoi L, Lam T, Vandvik PO, Hsu S, Bala MM, Schandelmaier S, Scheidecker A, Ebrahim S, Ashoorion V, Rehman Y, Hong PJ, Ross S, Johnston BC, Kunz R, Sun X, Buckley N, Sessler DI, Guyatt GH. Opioids for chronic noncancer pain: a systematic review and meta-analysis. Jama 2018;320: 2448–60.
[9] Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database Syst Rev 2013;8: CD004959.
[10] Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of

Health Pathways to Prevention Workshop. Ann Intern Med 2015;162: 276–86.
[11] Dekkers OM, Vandenbroucke JP, Cevallos M, Renehan AG, Altman DG, Egger M. COSMOS-E: guidance on conducting systematic reviews and meta-analyses of observational studies of etiology. Plos Med 2019;16: e1002742.
[12] Els C, Jackson TD, Hagtvedt R, Kunyk D, Sonnenberg B, Lappi VG, Straube S. High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database Syst Rev 2017;10:CD012299.
[13] Enthoven WTM, Roelofs P, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. Cochrane Database Syst Rev 2016;2:CD012087.
[14] Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. Pain Med 2008; 9:444–59.
[15] Friedmann N, Klutzaritz V, Webster L. Long-term safety of Remoxy (extended-release oxycodone) in patients with moderate to severe chronic osteoarthritis or low back pain. Pain Med 2011;12:755–60.
[16] Gould EM, Jensen MP, Victor TW, Gammaitoni AR, White RE, Galer BS. The pain quality response profile of oxymorphone extended release in the treatment of low back pain. Clin J Pain 2009;25:116–22.
[17] Hale ME, Zimmerman TR, Ma Y, Malamut R. Twelve-month, open-label assessment of long-term safety and abuse potential of hydrocodone extended-release formulated with abuse-deterrence technology in patients with chronic pain. J Opioid Manag 2015;11:425–34.
[18] Hauser W, Bernardy K, Maier C. Long-term opioid therapy in chronic noncancer pain. A systematic review and meta-analysis of efficacy, tolerability and safety in open-label extension trials with study duration of at least 26 weeks. Schmerz 2015;29:96–108.
[19] Henry D, McGettigan P. Epidemiology overview of gastrointestinal and renal toxicity of NSAIDs. Int J Clin Pract 2003;135:43–9.
[20] Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. Br J Anaesth 2018;120:1335–44.
[21] Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. The Clin J pain 2004;20:309–18.
[22] Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, Kroenke K, Bair MJ, Noorbaloochi S. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. JAMA 2018;319:872–82.
[23] Medicine Io. Relieving Pain in America: A Blueprint for Transforming, 2011.
[24] National Academies of Sciences E, and Medicine. Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. Washington, DC: The National Academies Press, 2017. doi: 10.17226/24781.
[25] Nicol AL, Hurley RW, Benzon HT. Alternatives to opioids in the pharmacologic management of chronic pain syndromes: a narrative review of randomized, controlled, and blinded clinical trials. Anesth Analgesia 2017;125:1682–703.
[26] Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. J Pain Symptom Manage 2008;35: 214–28.
[27] Portenoy RK, Farrar JT, Backonja MM, Cleeland CS, Yang K, Friedman M, Colucci SV, Richards P. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. Clin J Pain 2007;23:287–99.
[28] Sandner-Kiesling A, Leyendecker P, Hopp M, Tarau L, Lejcko J, Meissner W, Sevcik P, Hakl M, Hrib R, Uhl R, Durr H, Reimer K. Long-term efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of non-cancer chronic pain. Int J Clin Pract 2010;64: 763–74.
[29] Solomon DH, Husni ME, Libby PA, Yeomans ND, Lincoff AM, Luscher TF, Menon V, Brennan DM, Wisniewski LM, Nissen SE, Borer JS. The risk of major NSAID toxicity with celecoxib, ibuprofen, or naproxen: a secondary analysis of the precision trial. Am J Med 2017;130:1415–22.e1414.
[30] Walsh TL, Hanscom B, Lurie JD, Weinstein JN. Is a condition-specific instrument for patients with low back pain/leg symptoms really necessary?: the responsiveness of the Oswestry Disability Index, MODEMS, and the SF-36. Spine 2003;28:607–15.
[31] Wang N, Dong Y, Zhao L, Zhao H, Li W, Cui J. Factors associated with optimal pain management in advanced cancer patients. Curr Probl Cancer 2019;43:77–85.
[32] Ware JE Jr. SF-36 health survey update. Spine 2000;25:3130–9.
[33] Wen W, Taber L, Lynch SY, He E, Ripa S. 12-Month safety and effectiveness of once-daily hydrocodone tablets formulated with abuse-deterrent properties in patients with moderate to severe chronic pain. J Opioid Manag 2015;11:339–56.