Original Research Article

Negligible Analgesic Tolerance Seen with Extended Release Oxymorphone: A Post Hoc Analysis of Open-Label Longitudinal Data

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Abstract

Objective. To examine the development of analgesic tolerance in patients on oxymorphone extended-release (OxymER).

Design. Post hoc analysis of data from a previously conducted prospective 1 year multi-center open-label extension study in which patients were able to titrate as needed.

Patients. Sample of 153 hip and knee osteoarthritis (OA) subjects on OxymER. Primary analyses were limited to study completers (n = 62) due to the large amount of missing data for the noncompleters (n = 91).

Outcome Measures. Main outcome measures included OxymER doses (pill counts) and pain intensity ratings using a visual analog scale at monthly visits.

Results. There were significant dose increases from weeks 1 to 2 and 2 to 6 (P < 0.05). Doses stabilized around week 6, suggesting the completion of what we defined as “titration.” Both doses and pain ratings were stable when this titration phase was excluded from the analysis (P = 0.751; P = 0.056, respectively). Only 28% of the patients had any dose changes following this titration. While there was a significantly greater dose at week 52 compared with week 10 (P = 0.010), the increase in dose became insignificant after excluding four subjects who required two dose increases (P = 0.103).

Conclusions. The results showed that most of the titration/dose stabilization changes occurred within the first 10 weeks. A minority (28%) of subjects required dosage increases after this (defined) titration period. Pain reports stabilized statistically after 2 weeks. The findings of this post hoc analysis suggest a lack of opioid tolerance in the majority (72%) of these OA patients who completed this study following a defined titration period on OxymER.

Summary. This post hoc analysis of oxymorphone ER consumption in osteoarthritis pain vs pain report showed that most dose changes occurred during an initial “titration period” as defined. Following this titration few subjects increased dose and analgesia remained stable. These findings suggest a lack of longitudinal opioid tolerance in the majority of those OA subjects who completed the trial.

Key Words. Opioid Tolerance; Nonmalignant Pain; Osteoarthritis

Introduction and Review

The development of tolerance with chronic opioid use remains a contentious issue and central to the debate
over the appropriateness of long-term opioid therapy [1,2], yet tolerance remains one of the least understood phenomena in human analgesic research. Ambiguity about opioid tolerance stems, in part, from semantics. There are several types of tolerance that occur in humans: innate/genetic, pharmacokinetic/metabolic, pharmacodynamic, learned/behavioral, contextual/sociologic, etc. [3–5]. None of these types of tolerance have been formally studied in a clinically relevant fashion (e.g., over the course of months and even years, in clinically relevant doses, in well defined diagnoses, etc.) [2].

An historical assumption is that human tolerance develops in all chronic opioid dosing; however, this assumption, the prevalence, the extent and the true incidence of opioid tolerance has not been proven [2,6–8]. In cancer related pain, the question of tolerance was not considered a clinically relevant issue until recently, since improvements in cancer treatment have thankfully provided the opportunity to view oncology patients as “chronic” pain sufferers in many cases [9,10]. On the other hand, in chronic noncancer pain, tolerance is considered more salient, due to the concern that liberal and frequent dose escalation (theoretically for the remainder of the patient’s life) is not a realistic possibility [2,7,11]. Tolerance is therefore the natural subject of much discussion in the pain field [6,12–15]. If the incidence of tolerance were to prove to be significant in opioid therapy for chronic “benign” conditions, then it is critical to assess if it is an absolute and/or a steadily progressive process as this would hypothetically contraindicate the use of opioids in persistent pain [2,7,12]. If it is an incomplete phenomena, a remitting phenomena, or if the analgesic effect “plateaus” like some of the drug’s other effects [13,14,16], or if it only occurs in a subset of patients, then tolerance would not be a compelling contraindication for chronic use [17].

Tolerance is not unique to opioids, and occurs in many other classes of medications [6,17]. It is clear that tolerance develops to a variety of effects associated with opioids in animal models [5,6,18,19], in cancer pain [16,20,21], in acute experimental pain [22–24], and in street use [24–26]. Tolerance has even been suggested to occur in a-operatoratively with apparent post-op increases in pain intensity and opioid consumption [27,28]. The experimental work studying human opioid tolerance has been primarily carried out in healthy volunteers in short duration, high-dose experiments [29]. This work is not generally relevant to real clinical situations, specifically to long-term therapy in chronic nonterminal pain conditions [13,15,29,30]. There is a modest literature addressing the question of efficacy of opioids over “clinically relevant” periods (although defining clinically relevant in this context is debatable) [31–38]. However, to date there are no systematic studies of tolerance over similar clinically relevant periods (e.g., “months” for our purposes), and the statistical methodology for studying this phenomena has not been developed.

The incidence of opioid tolerance has been in some measure addressed by several surveys. For example, research in cancer subjects reveals that 42–75% developed detectable tolerance [39,40]. A somewhat lower incidence of tolerance was reported in a well-designed prospective study of chronic noncancer subjects, in which 43% of subjects needed an increase in opioids over the course of the study [41]. Tolerance does not occur universally or among certain populations, and under certain conditions it may not develop, even over extended periods of time [6,13,16,17,42]. After an early dose titration (which is distinct from tolerance), patients may “plateau” at a dose for prolonged periods of time [13,14,21].

Pain itself may influence the rate and incidence of the development of tolerance [5,14,43–45], and the presence of persistent pain may actively reduce the tolerance or dependency producing properties of opioids [46]. When procedures such as nerve blocks or surgery (e.g., cordectomy) abruptly lower nociceptive input, there may be a substantial decline in the opioid dose required to treat the pain complaint [47,48], and patients who are normally tolerant to opioid side effects, may develop severe side effects following such procedures [47,48]. In cases of persistent pain, there may be a change in the underlying nociceptive process (e.g., disease progression in cancer patients), which causes an increased opioid requirement, mimicking tolerance [21,49–51]. Results of one study indicate that more than 60% of subjects said to be developing “tolerance” were attributed to such a process [8]. Thus, in conducting research on opioid therapy, it is important to document disease progression prior to attributing dose escalation to apparent tolerance, although this may in fact be extremely difficult in the nebulous diagnoses and vague pathophysiologies encountered in chronic pain populations [52]. Obviously, the concept of tolerance is multi-faceted and the authors agree that “the complexity of opioid tolerance parallels the complexity of pain itself” [29].

The mechanisms of opioid tolerance are apparently very complex, and involve not only desensitization and down regulation of receptors [18,53], but also dynamic regulation by feedback mechanisms, linked receptors, receptor genesis, second messengers, and metabolic enzyme systems [6,54,55]. The n-methyl-D-aspartate (NMDA) subtype of the glutamate receptor seems to be very important in the development of tolerance [18,56–61]. NMDA antagonists block the development of tolerance, cross-tolerance, and dependence [24,57,58,62–64], but this effect may be modality specific [23]. Protein kinase-C may potentiate the NMDA response by increasing the probability of channel opening and by reducing the voltage dependence producing properties of opioids [46]. When procedures such as nerve blocks or surgery (e.g., cordectomy) abruptly lower nociceptive input, there may be a substantial decline in the opioid dose required to treat the pain complaint [47,48], and patients who are normally tolerant to opioid side effects, may develop severe side effects following such procedures [47,48]. In cases of persistent pain, there may be a change in the underlying nociceptive process (e.g., disease progression in cancer patients), which causes an increased opioid requirement, mimicking tolerance [21,49–51]. Results of one study indicate that more than 60% of subjects said to be developing “tolerance” were attributed to such a process [8]. Thus, in conducting research on opioid therapy, it is important to document disease progression prior to attributing dose escalation to apparent tolerance, although this may in fact be extremely difficult in the nebulous diagnoses and vague pathophysiologies encountered in chronic pain populations [52]. Obviously, the concept of tolerance is multi-faceted and the authors agree that “the complexity of opioid tolerance parallels the complexity of pain itself” [29].
systems, which may in turn alter drug effect [6,69]; for instance cholecystokinin (CCK), dynorphin, calcitonin gene-related peptide (CGRP) [69], morphine-3-glucuronide [70], GABA<sub>a</sub> [71], melancortin [72], etc. Cytokines and prostaglandins are also involved in tolerance [73]. There is no evidence that changes in extra-cellular metabolism or drug distribution are primary factors in the development of tolerance. There is some evidence that some aspects of “tolerance” may actually be an increased sensitivity to pain, so called “opioid hyperalgesia” [24,74], and the distinction between these two apparently related concepts is by no means entirely clear. The critically important psychosocial and contextual vectors influencing opioid use, dose escalation and “behavioral tolerance” are beyond the scope of this introduction.

Basic science research has provided useful insights into the mechanisms of tolerance [6,18,19,75,76]. In most animal models, tolerance appears to develop at some specific rate, regardless of drug or dose, and the decrement in analgesic effect may be best described by an exponential decay function [3]. However, two animal studies have looked at tolerance in the intermediate term, and suggest that “long-term morphine administration maintains an analgesic effect without emergence of analgesic tolerance” [46,77], the “Analgesic Plateau.” Prior exposure to an opioid may exert a long term influence on the development of future tolerance through an up-regulation of neuronal glucocorticoid receptors within the dorsal horn [78].

In animal models, the loss of analgesic effect in response to chronic opioid exposure can be observed following all routes of administration [6,18]. In humans, however, the route of administration and timing of delivery appear to be important issues specifically in the development of tolerance to analgesic effects [29,47]. The dose of opioid may not influence the rate or degree of tolerance in humans [79], although there is evidence that more potent agonists may actually produce less tolerance than less-potent opioids [3]. The tolerance to opioid effects other than analgesia (e.g., respiratory depression, sedation, nausea, pruritis) develop at different rates [14,29], and the rate at which tolerance to any effect develops may vary greatly between individuals [13,80,81]. Differential types of tolerance may develop to different formulations or delivery systems (e.g., intrathecal [82]).

In a recent longitudinal prospective open-label registry study of an oxycodone CR compound combining the results of five trials, the question of tolerance was raised, with recommended times of 8:00 and 20:00 equally divided doses on a twice daily schedule (Q12H). Subjects were instructed to take the study medication in jects transferring into the study from another open-label blind-phase of the study were started at the lowest dose experience. Subjects who took an active agent during the initial dosage was determined by previous study methods. Subjects transferring into the study from another open-label study began the study with their last recorded dosage. Subjects were instructed to take the study medication in equally divided doses on a twice daily schedule (Q12H) with recommended times of 8:00 and 20:00 ± 1 hour. Dose adjustments were made in response to inadequate pain relief and/or unacceptable side effects. Oxymer dose was calculated by pill counts at monthly visits and pain intensity was assessed at each visit using a 100 mm
visual analog scale. All subjects were administered 20 mg tablets of OxymER as it was the only available dosage strength available during the study [34].

**Statistical Analyses**

All data were analyzed using SPSS 16.0. Descriptive statistics were used for presenting the demographic information for both the study completers and the noncompleters. Demographic group differences were analyzed using independent samples t-tests and nominal data was analyzed using Chi-square and Fisher's exact test (for data with cells less than 5). Repeated-measures analyses of variance (ANOVA) were used to examine possible differences in dose and pain over time for the completers. A cumulative event curve was used to show the actual probability of subjects reaching a stable dose of OxymER (i.e., not needing any further dose escalations) at each study visit. Individual regression analyses were used to obtain slopes for both dose and current pain ratings while independent samples t-tests were used to compare the slopes. Chi-square analyses were conducted in order to evaluate whether or not subjects who had received placebo during the randomized portion of the study were more likely to need dose escalations during the open-label portion of the study than those who had received OxymER.

**Results**

**Demographics**

Descriptive information and statistics comparing demographic information of the study completers and noncompleters are presented in Table 1. There were no significant differences between the completers and noncompleters for ethnicity, age, or baseline ratings of current pain intensity. The distribution of males and females trended toward significance ($P = 0.054$). There were similar, nonstatistically significant ($P = 0.568$), proportions of individuals with previous opioid experience in both the completers (0.72) and noncompleters (0.68); approximately 1/3 of the subjects were opioid naive in both groups. The majority ($n = 49$ of 91, 53.8%) of the noncompleters withdrew due to nonserious adverse events. The reasons for the remaining withdrawals were: 13.0% “minimal therapeutic effect” (despite dose adjustments); 10.9% serious adverse events (SAE); 10.8% “other” (site closed by sponsor and patient relocation); 6.5% noncompliance; 4.4% patient request; and 1.1% investigator withdrawal of patient. It is important to note that the majority of the SAEs were not considered treatment related; five were suspected as being treatment related, 10 unrelated, and five unlikely related [34]. Only a small percentage (7.8%) of subjects withdrew “because of insufficient therapeutic effect” [34]. The completers may predominately represent those who did not have side effects, rapidly developed tolerance to side effects, and/or had excellent and early pain relief. The design and data from this trial is insufficient to address these possibilities, but with a more specific design these factors could be assessed.

**Dose and Pain Ratings**

Descriptives of the doses and current pain ratings for the completers and noncompleters are included in Tables 2 and 3, respectively.

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**Table 1** Subject demographics

| Subject demographics characteristic | Completers N = 62 | Noncompleters N = 91 | Statistics* |
|-------------------------------------|------------------|----------------------|-------------|
| Sex, n (%)                          |                  |                      |             |
| Women                               | 44 (71.0)        | 52 (56.52)           | $\chi^2 = 3.489, P = 0.062$ |
| Men                                 | 18 (29.0)        | 40 (43.48)           | Fisher’s exact test, $P = 0.402$ |
| Ethnic origin                       |                  |                      |             |
| White                               | 52 (83.9)        | 79 (86.8)            |             |
| Black                               | 8 (12.9)         | 7 (7.7)              |             |
| Hispanic                            | 1 (1.6)          | 4 (4.4)              |             |
| Portuguese                          | 1 (1.6)          | 0 (0)                |             |
| Asian                               | 0 (0)            | 1 (1.1)              |             |
| Age, mean years ± SD                | 60.26 ± 9.42     | 59.80 ± 10.50        | $t(151) = -0.281, P = 0.779$ |
| Range                               | 41–82            | 40–84                |             |
| Baseline pain                       | 47.50 ± 24.72    | 52.80 ± 22.03        | $t(151) = 1.391, P = 0.166$ |
| Range                               | 2–93             | 4–98                 |             |
| Previous exposure, n (%)            |                  |                      | $\chi^2 = 0.325, P = 0.568$ |
| Placebo                             | 17 (27.9)        | 29 (32.2)            |             |
| Opioid                              | 44 (72.1)        | 61 (67.8)            |             |

* No significant differences between groups.
In order to properly assess for tolerance in a study, we first needed to establish the initial dose stabilization or "titration" period. As there was no formal period identified in the protocol for titration to analgesic effect, and the study physicians were allowed to freely titrate (as described above) to adequate analgesic effect and tolerable adverse events, we have determined and defined the titration period statistically by finding the point at which the average dose initially stabilized. Thus, the doses were examined using a repeated-measures ANOVA (weeks: 1, 2, 6, 10, 16, 22, 28, 34, 40, 46, and 52) and are depicted in Figure 1. Mauchly's test indicated violation of the sphericity assumption, so a Greenhouse-Geisser adjustment was used. The results indicated a significant change in dose over time ($F[3, 181] = 16.396, P = 0.000$). Follow-up repeated measures contrasts showed significant dose increases from weeks 1 to 2 ($F[1, 59] = 10.083, P = 0.002$) and from weeks 2 to 6 ($F[1, 59] = 6.268, P = 0.015$). All remaining contrasts were nonsignificant with $P$ values $> 0.05$ signifying that the doses were stable after week 6. Pain and dosage data was only acquired at 1, 2, 6, and 10 weeks in the early portion of the trial, the doses statistically stabilized after 6 weeks and the first available data point after this is 10 weeks: therefore, for the purposes of this analysis we define 10 weeks as the end of the "titration period." Ten weeks is certainly enough time to achieve titration, even in the chronic outpatient scenario. Given this definition and assumption, we chose week 10 to represent the baseline dose and pain levels for the tolerance analysis and defined all previous weeks as titration and dose stabilization. There may have been some initial “tolerance” occurring in some subjects during this time period, but it is impossible to separate that from titration issues (at least with this sporadic data base), so the long "titration" period was selected to assure any titration effect (which obviously contaminates a tolerance analysis) was hypothetically complete.

**Table 2** Descriptives for dose and current pain ratings by visit for 1-year completers

| Time   | Dose (n = 60) | Current pain (n = 62) |
|--------|---------------|-----------------------|
|        | Mean    | SD     | Mean   | SD     |
| Baseline | n/a   | n/a   | 47.50  | 24.72  |
| Week 1  | 42.67  | 10.71 | 27.69  | 24.57  |
| Week 2  | 48.33  | 16.17 | 22.02  | 20.62  |
| Week 6  | 52.00  | 19.55 | 22.45  | 22.03  |
| Week 10 | 55.67  | 20.86 | 21.92  | 22.66  |
| Week 16 | 57.67  | 21.18 | 19.21  | 22.60  |
| Week 22 | 57.00  | 22.35 | 22.53  | 24.85  |
| Week 28 | 57.67  | 22.43 | 18.44  | 22.33  |
| Week 34 | 59.00  | 24.82 | 20.32  | 22.56  |
| Week 40 | 59.67  | 25.91 | 20.74  | 22.94  |
| Week 46 | 60.33  | 25.91 | 21.02  | 25.70  |
| Week 52 | 61.00  | 25.89 | 20.10  | 22.96  |

**Table 3** Descriptives for dose and current pain ratings by visit for noncompleters

| Time | Dose | Current pain |
|------|------|--------------|
|      | n    | Mean | SD | Mean | SD |
| Titration |      |      |    |      |    |
| Baseline* | 91   | n/a  | n/a | 53.34 | 21.53 |
| Week 1 | 62   | 41.59 | 7.45 | 35.50 | 24.62 |
| Week 2 | 48   | 47.31 | 15.35 | 33.12 | 23.04 |
| Week 6 | 28   | 48.13 | 19.04 | 30.40 | 23.64 |
| Post-titration | |      |    |      |    |
| Week 10 | 15  | 56.47 | 20.29 | 30.65 | 21.52 |
| Week 16 | 12  | 60.63 | 20.75 | 20.64 | 15.43 |
| Week 22 | 9   | 64.63 | 20.66 | 20.64 | 18.41 |
| Week 28 | 7   | 65.00 | 20.70 | 20.00 | 20.51 |
| Week 34 | 6   | 62.86 | 21.38 | 30.57 | 29.56 |
| Week 40 | 6   | 68.57 | 19.52 | 30.33 | 17.99 |
| Week 46 | 3   | 80.00 | —    | 48.00 | —   |
| Week 52 | 0   | —    | —    | —    | —   |

* Pain rating data was missing for one subject.

**Pain Ratings**

Pain ratings were examined using a repeated-measures ANOVA (weeks: 0, 1, 2, 6, 10, 16, 22, 28, 34, 40, 46, and 52) and are depicted in Figure 1. Mauchly’s test indicated violation of the sphericity assumption, so a Greenhouse-Geisser adjustment was used. The results showed that pain ratings differed significantly over time ($F[8, 444] = 2.036, P = 0.045$) if the initial titration period was included in the analysis (the trial showed significant

![Figure 1 Mean pain intensity ratings (0–100 mm visual analog scale) for current pain and mean dosages (mg) at each visit.](https://academic.oup.com/painmedicine/article-abstract/11/8/1198/1855635)
improvement in pain with the intervention. Repeated measures contrasts during follow-up indicated significant pain decreases from baseline to week 1 (F[1, 61] = 33.727, P = 0.000) and from week 1 to week 2 (F[1, 61] = 8.156, P = 0.006). All remaining contrasts for pain were nonsignificant with all P values > 0.05 suggesting that the pain ratings were stable after week 2. However, when the “titration period” was excluded from the analysis the results showed that pain ratings did not differ significantly over time (F[6, 366] = 0.574, P = 0.751) meaning that benefit achieved during titration continued for the duration of the year.

Dose

Doses were also examined using a repeated measures ANOVA (weeks: 10, 16, 22, 28, 34, 40, 46, and 52). Mauchly’s test indicated violation of the sphericity assumption, so a Greenhouse-Geisser adjustment was used. The results indicated nonsignificant change in dose over time (F[3, 162] = 2.642, P = 0.056). For the tolerance analysis we used a paired-samples t-test to examine possible differences in doses between weeks 10 and 52 (final week in the study). The result (t[1, 59] = 2.654, P = 0.010) showed a significant dose difference when comparing week 10 to week 52, with the dose at week 10 (M = 55.67, SD = 20.86) less than that at week 52 (M = 61.00; SD = 25.89), suggesting that tolerance is present after the titration period. That is, a significantly higher dose (compared with baseline = week 10) was needed to maintain statistically stable analgesia at week 52.

However, 43 (71.7%) of the completers had no change in dose following the titration period. Of the remaining 17 (28.3% of total), dose changes were as follows: 13 of the 17 (76.5%) had one increment change and 4 of the 17 (23.5%) had two increment changes resulting in a total of 21 increment dose changes. While there was a significantly greater dose at week 52 compared with week 10, the increase in dose became insignificant when we excluded the 4 patients with >1 dose change (P = 0.103). Thus, a minority of the sample contributed to the apparent tolerance effect. Furthermore, any tolerance effect could possibly be confounded by the manifestation of worsening OA symptoms, thus not tolerance. Our analysis would suggest that the remainder of the sample (72%), as defined, did not demonstrate tolerance.

In the study by McIlwain and Adieh all subjects (intent-to-treat population) were included in the analyses that lead to their assertion that there was no evidence of analgesic tolerance to OxymER [34]. This assertion was partially based on the fact that the median daily dose of OxymER was 40 mg at all visits. This finding would certainly lead to the conclusion of a lack of tolerance. However, the authors did not base this claim solely on the descriptive analysis of medians. They also based their claim on the obtained distribution of means stating, “The modest increase in mean daily dose of study medication is related to the disproportionate withdrawal of opioid-naïve entering at 40 mg/d (i.e., withdrawal of patients who entered at the lower daily doses contributed to the increase in the mean, patients entering at higher doses maintained a stable dose).” In our analyses of the data, excluding the noncompleters, we obtained a similar dispersion of means. The mean doses they reported for weeks 1 (M = 48) and 52 (M = 62) are similar to the means we obtained at weeks 1 (M = 43) and 52 (M = 61). Furthermore, we also found the median daily dose to be 40 mg at each visit. And we also observed a visual trend for the means to increase. Thus, we analyzed the means and found tolerance to occur, at least in a minority of subjects (see results reported above). Also, the majority (59%) of the completers that had a dose change were those with previous opioid experience.

Time to Dose Stabilization

The cumulative event curve (Figure 2) shows that the majority of subjects (72%) did not need further dose escalation following the titration phase. Furthermore, 82% of the subjects reached stability by week 16, 85% by week 22, 90% by week 28, 92% by week 34, 95% by week 40, 97% by week 46, and 98% by week 52.

Dose and Pain Rating Slopes

The mean slopes for dose and pain ratings were calculated for weeks 10–52 (after titration), did not differ t(98) = 1.421, P = 0.159. These findings suggest a lack of tolerance when factoring out the titration period.

Opioid-Experienced vs Opioid-Naïve

As mentioned previously, approximately 1/3 of both completers and noncompleters were opioid-naïve. We examined for possible dose increase during the open-label portion of the study by previous status in the randomized controlled trial. When including data from the titration period of the study those who previously received placebo trended toward having a higher proportion of subjects (0.65) needing more dose escalations than did those who had received OxymER (0.37), but the difference was not statistically significant (\( \chi^2 = 3.722, P = 0.054 \)). And when the titration period was excluded from the analyses the need for dose escalation did not vary by previous status (placebo and OxymER); \( \chi^2 = 0.566, P = 0.452 \). The proportion of placebo and OxymER subjects needing dose escalations was 0.35 and 0.26, respectively. That is, although many opioid-naïve subjects dropped out due to opioid-related AEs during titration, those who established a stable dose remained at that dose.

Noncompleters, Dose

Paired-samples t-tests were used to examine the differences between subjects’ doses at week 1 and their final visit, week 2 and final visit, week 6 and final visit, and week 10 and final visit. Mean final doses were significantly greater than mean doses during the titration period; at week 1 t[1, 53] = −5.339, P = 0.000, week 2 t[1, 51] = 3.432, P = 0.001, and week 6 t[1, 29] = 2.112, P = 0.056.
\[ P = 0.043 \]. Mean final doses compared to week 10 (following titration) were not statistically significant (\( t[1, 16] = 1.461, P = 0.163 \)). This pattern of results is similar to that found for the study completers.

**Discussion**

In this *post hoc* analysis of a longitudinal effectiveness/safety opioid trial, the majority (72%) of the osteoarthritis subjects who completed the trial did not show tolerance (defined as a dosage increase after initial titration to maintain adequate analgesia). A minority (28%) did need modest dose escalations to maintain acceptable analgesia, but they too seemed to develop a response plateau (or equilibrium level; [84]) later than our defined “titration period” (92% by 28 weeks). Mean pain ratings were stabilized in all subjects after week 2. Thus, by the statistical analysis we selected (ANOVA with repeated measures for pain levels and for dose over time) there is a statistically significant change in average dose to maintain pain at post titration levels; however, this effect was limited to a minority of the subjects. We conclude on the basis of this data, given these assumptions and the limitations of the data base, that opioid tolerance was nonsignificant in the majority (72%) of study completers.

The time selected for titration to analgesic effect is critical to the analysis [30]. We defined the titration period to end at week 10, based on statistical methods to assess the first inflection point that indicates reasonable analgesic effect had been achieved. If 16 weeks were defined as the end of the titration, then 87% did not demonstrate the need for any dose escalations and after 28 weeks 92% did not require dose escalation. There is no consensus in the literature as to what constitutes a reasonable, average clinical time for such a titration for any opioid compound or formulation (including OxymER), but it is clear that there should be a presumed initial period of dose escalation leading to dose stabilization (i.e., titration), which must be excluded from an analysis of true analgesic tolerance. It is conceptually critical that a long enough period be selected so that titration effect cannot reasonably contaminate the tolerance analysis, thus we chose a long “titration” period to assure this or any other early dose stabilization effects would not compromise the intent. In the future, definitive models of this methodology (with considerably greater data density) could be prospectively defined, or careful pilot work with any specific compound could (arbitrarily) indicate a specific, set titration time.

Our decision to not include data from noncompleters is open to debate, but clearly the concept of using last observation carried forward defeats the ability to answer the question as it creates the appearance of “no tolerance” in the subset that does drop out [85]. On the other hand, if subjects were dropping out due to an emerging lack of analgesic effect, excluding noncompleters may overlook true drug tolerance in that subset. The answer may be very frequent pain and dose measurements (ideally, daily), not carrying forward data, and detailed exit interviews to determine the reason for drop out. Although liberal dose escalation was employed in this study, only 20 mg dose increments were available. Utilizing a greater range of possible doses may minimize drop out due to lack of analgesia and/or difficulty tolerating side effects (e.g., going from 20 to 40 mg), thus with greater retention we may improve our ability to detect possible tolerance in those who otherwise would drop out.

\[ \text{Figure 2 Cumulative percentages of patients reaching dose stabilization at each visit.} \]
Anecdotal evidence suggests a lack of significant tolerance may be a class effect of mu agonists [30], and not unique to this compound. There is a critical need to include uniform protocols to assess this hypothesis in other drugs in this class. This apparent lack of tolerance may be specific to the population studied (i.e., older, mostly female, mostly Caucasian subjects with OA of hip or knee). For instance, older subjects may have a reduced rate of tolerance development [86]. It will be important to study the development of tolerance in other populations (e.g., age, gender) and different diagnoses and pain mechanisms (e.g., nociceptive, neuropathic, central pain, etc.) [75]. It is quite possible that other populations and models may show differential tolerance effects.

This post hoc analysis was based upon data derived from a study which had an original protocol that was not designed to investigate the question of tolerance, but was a standard drug registry trial designed to test long term effectiveness and safety [34]. An appropriate design to test the tolerance hypothesis certainly would be a controlled prospective study, but this design would face substantial practical obstacles. For instance, the ethics and subject retention of long-term placebo control in a chronic pain trial might prove untenable. Alternatively, a practical and more effective design would incorporate frequent pain assessment and allow completely free dose adjustments with a greater range of dose choices to achieve adequate and consistent pain relief (i.e., subset of any population in which adequate pain control with opioids is possible). The most prominent limitations of this Phase III data set are infrequent pain assessments and limited dose choices. A proper, prospective, working definition of terms such as “tolerance,” “adequate pain control,” etc. are obviously minimal requirements to authoritative trials. A definitive design to properly study tolerance will likely require a large number of subjects, so how to fund such work becomes an important practical question. Statistical methodology must be prospectively determined, yet best or even adequate methodology is as yet uncertain. New and better methodologies to formally test some aspects of tolerance are becoming available [87].

In this and another recent post hoc analysis [30], it does not appear that analgesic tolerance was a significant factor in the majority of study completers. This is the only study to date to utilize parametric statistics to assess tolerance and to present those detailed results. The study by Portenoy et al. [30] included parametric statistics but the specific findings (i.e., what statistical difference[s] in doses occurred [if any] and at which time points) unfortunately were not reported in the results. However, neither of these prospective open-label extension trials was specifically designed to assess tolerance. It is imperative that future longitudinal opioid studies include prospective methodologies that are adequate to address the crucial question of human opioid tolerance over relevant clinical periods.

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