Embeda™: morphine sulfate extended-release capsules with sequestered naltrexone, a novel opioid formulation for the treatment of chronic pain

Chronic opioids are often used in the management of chronic osteoarthritis pain. Embeda™ (Alpharma Pharmaceuticals, NJ, USA) is a novel and recently approved (in the USA) extended-release formulation of morphine. It combines morphine with a sequestered, inner core of naltrexone (an opioid antagonist) that is not significantly absorbed when the capsule is taken as directed (whole). Should the capsule be tampered with, such as crushing or chewing, the naltrexone will be released, absorbed and counter the opioid effect. It is hoped that this combination morphine product will help deter patients or addicts from inappropriate use of opioids. Short-term clinical trials of Embeda demonstrate analgesia and improved physical functioning among patients with chronic pain related to osteoarthritis. This article reviews the chemistry, clinical efficacy and possible role of Embeda for the management of chronic pain.

KEYWORDS: abuse deterrence ■ chronic pain ■ extended release ■ naltrexone ■ opioid

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Opioids have been known to have analgesic properties for thousands of years. The chronic use of opioids for the treatment of chronic noncancer pain has only lately seen increased medical practice [1] owing to a relative lack of efficacy data, until recently, from well-controlled studies. The efficacy of morphine, oxycodone and oxymorphone in extended-release dosage forms has been demonstrated in randomized, placebo-controlled, double-blind clinical trials for the treatment of pain related to osteoarthritis, low back pain and neuropathic pain [2–6]. The use of chronic opioid therapy in the treatment of chronic cancer pain has been well established as safe and effective in countless clinical trials around the world [7]; however, the use of chronic opioids for the management of chronic noncancer pain has been associated with misuse by patients, pseudopatients, recreational drug users and individuals with an opioid addiction disorder [8]. It has been estimated that the nonmedical use of prescription opioids has increased fourfold in the last 20 years with prescription opioid abuse more prevalent than most street drugs and similar to trends observed for marijuana [9]. Since chronic opioid therapy is beneficial for some pain patients there has been an interest in developing opioid dosage forms that provide opioid analgesia yet are difficult to divert to nonmedical uses.

Chronic noncancer pain, such as low back pain and osteoarthritis pain, affect up to 20% of the population of western countries [1]. With the introduction of extended-release opioid products [10] the physician has some tools to combat pain and suffering among some patients with chronic pain. However, the primary physician also has to attempt to limit the diversion of prescribed opioid medications and, thus, protect the public. There are many methods advocated to help diminish the risk of prescription opioid abuse. First, all physicians are encouraged to complete a full pain history and physical examination, including a pain diagnosis and differential diagnosis. Next, patients should be initially treated with nonopioid analgesics and nondrug treatments, such as physical therapy, massage, electrical stimulation and cognitive therapies. Physicians are encouraged to treat patients with interventional injective therapies when appropriate. If chronic opioid therapy is required, the treating physician should complete screening tools to identify patients at risk for opioid abuse prior to initiation of therapy [11]. Patients may be asked to sign medication agreements to help ensure compliance, and random and intermittent urine drug screens will help identify compliance with prescribed treatment [12]. All patients should be considered to have a 'trial' of opioid medications and, when opioid therapy is unsuccessful or associated with unacceptable side effects, the opioids should be discontinued and other treatments instituted [13]. Recent guidelines have suggested that physicians should carefully re-evaluate patients who require high doses of opioids, defined as greater than 200 mg daily of morphine [14].

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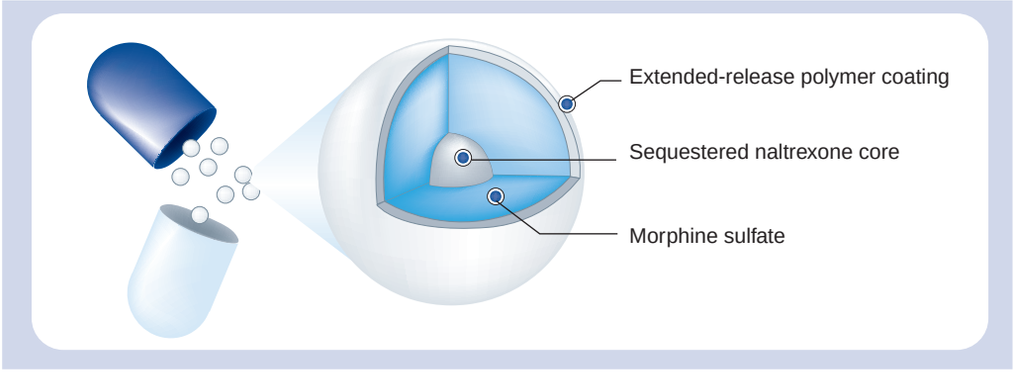

Figure 1. Architecture of Embeda™ extended-release capsule.
Data taken from [16].

In addition to the previously stated measures, pharmaceutical companies have developed novel formulations of opioids designed to be more difficult for a patient or addict to abuse yet will still provide analgesia [15]. Embeda™ (Alpharma Pharmaceuticals, NJ, USA; extended-release morphine with sequestered naltrexone) is such a product and, thus, presents a possible breakthrough in the safe use of chronic opioids for legitimate patients with chronic pain. The use of an opioid agonist with a sequestered opioid antagonist is an advance in formulation technology since this product (with an internal sequestered core of naltrexone that, if the product is tampered with, is designed to be released and reduce any opioid euphoria) may deter abuse not only by the oral route, but also by the parenteral route of drug use. In early clinical trials, Embeda was referred to as ALO-01 and Kadian® NT.

The purpose of this article is to review the chemistry and clinical efficacy in the treatment of chronic pain of Embeda, a novel opioid formulation designed to reduce the risk of opioid abuse.

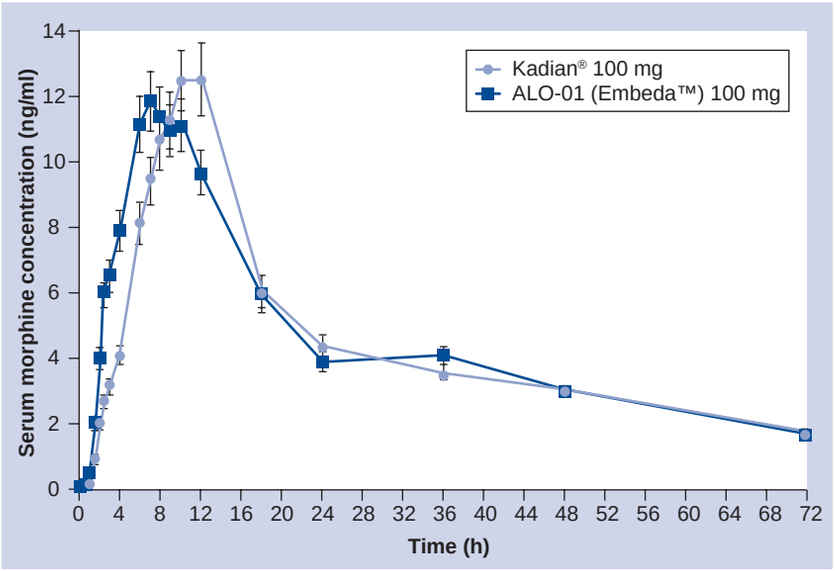

Figure 2. Mean serum morphine concentration–time data after a single dose of Embeda™ 100 mg (morphine sulfate extended release with sequestered naltrexone hydrochloride) and Kadian® 100 mg (morphine extended-release) to 34 fasted, healthy subjects demonstrating bioequivalence.
Data taken from [16].

Chemistry & pharmacokinetics

Embeda is a recently approved novel, extended-release capsule of morphine sulphate (Figure 1) that combines morphine (surrounded by an extended-release polymer coating) with a sequestered, inner core of naltrexone. The active analgesic medication in Embeda is morphine. Embeda capsules contain pellets of morphine (the active analgesic) and naltrexone in a ratio of 25 mg:1 mg. If the capsule is swallowed whole, morphine is released over a sustained period of time, with little or no appreciable release of the opioid antagonist, naltrexone, which remains sequestered in the core of each pellet. If the capsule pellets are crushed or chewed (typical behavior for addicts to obtain dose dumping of extended-release opioid compounds and achieve high morphine levels) both morphine and naltrexone are released and absorbed in immediate-release form. Similarly, when the capsule pellets are crushed and then dissolved in common solvents to extract the morphine for intravenous (iv.) injection, the sequestered naltrexone is completely released. In the case of product tampering, the released naltrexone would be expected to mitigate the increased psychic effects of morphine under conditions of attempted abuse.

The pharmacokinetics of the active ingredient, morphine, are similar to other morphine extended-release products. Under fasted conditions, untampered Embeda is bioequivalent to Kadian (morphine sulfate extended release),

which was approved in the USA in 1996 (FIGURE 2). Dosing is suggested at once or twice daily and should not occur more frequently than every 12 h.

Following single doses of Embeda to healthy volunteers, approximately 50% of the dose reaches the systemic circulation after 8 h [101]. However, as with all oral opioids, between 60 and 80% is first cleared in the liver. Although the 90% confidence intervals for the log-transformed ratios of AUC_{0-t}, AUC_{inf} and C_{max} of Embeda and Kadian are within the 80–125% bioequivalence range, the median time to peak plasma morphine concentration (T_{max}) for Embeda is 7.5 h compared with Kadian at 10 h [101]. When single doses of either crushed Embeda, whole Embeda or morphine solution were given to recreational drug users, the maximum plasma morphine concentration and time to maximum morphine concentration were very similar for crushed Embeda capsules and morphine immediate-release solution [101], while the whole Embeda capsules yielded much lower maximum morphine concentrations. The ingestion of food slowed the rate of absorption, but did not affect the total bioavailability of morphine. Following a single dose of whole Embeda the elimination half-life is 29 h [101]. When Embeda is coingested with 240 ml of 40% ethanol, it is released at a substantially faster rate compared with Embeda consumed with water [16,101], the C_{max} is increased twofold (range: 1.4- to 5-fold) and the median time to peak concentration (T_{max}) is 5 h earlier.

The pharmacokinetics of the active antagonist, naltrexone, are clearly dependent on whether the capsule is taken whole (as directed) or crushed (as may occur with tampering). When taken whole, naltrexone contained in the Embeda capsule is not appreciably absorbed. This is critical to the purpose of this product because any significant absorption of naltrexone could possibly reverse the morphine analgesia or cause opioid withdrawal in a patient on chronic opioid therapy [17].

The oral bioavailability of naltrexone in Embeda was studied in 32 opioid-experienced, nondependent drug-user subjects [18]. Subjects each received whole and crushed Embeda 120 mg morphine (containing 4.8 mg naltrexone HCl), 120 mg morphine sulfate solution and placebo in a four-way crossover study separated by a 2–3-week washout period. Naltrexone remained sequestered in the Embeda capsule when taken whole (intact). Negligible amounts of naltrexone were detected in five out of 32 subjects after Embeda whole capsule treatment (with only one value above the limit of quantitation reported for each of the five subjects). By contrast, plasma naltrexone was detectable in all subjects after treatment with Embeda crushed pellets, with naltrexone exposure levels comparable to those expected after oral immediate-release naltrexone. This study demonstrated that, when tampered, Embeda capsules release the sequestered naltrexone as designed, thereby rendering the dosage form compatible with the aim of abuse deterrence. In clinical trials where up to 860 mg Embeda was taken twice daily for 12 months, 89% of patients at steady state had no detectable naltrexone levels, while 11% had extremely low plasma levels (4–145 pg/ml) that would be unlikely to affect analgesia or produce opioid withdrawal [101]. The ingestion of food did not affect the sequestration of naltrexone [101].

Pharmacodynamics

The pharmacodynamics of this unique combined opioid agonist:sequestered opioid antagonist dosage form have been investigated in two volunteer studies among nondependent recreational opioid users. Critical to the success of any abuse-deterrent medication is that the capsule swallowed whole does not interfere with analgesia, and that the capsule swallowed after

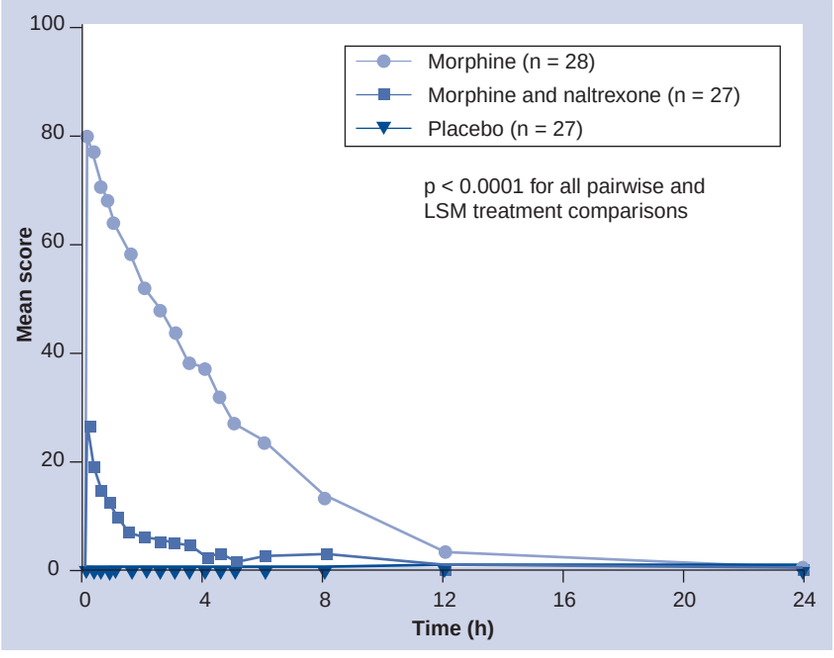

Figure 3. Mean score to the question 'How high are you now?' is reduced among recreational opioid users with combination of intravenous naltrexone and intravenous morphine, compared with intravenous morphine alone.
LSM: Least-squares means.
Data from [16].

crushing does mitigate opioid-induced euphoria. This is very important if the product is to truly act as a deterrent to product tampering (such as capsule crushing or iv. injection. Two volunteer studies among subjects with a history of recreational opioid drug use addressed this issue. First, a randomized, double-blind, placebo-controlled, three-way cross-over study was conducted in 28 subjects with a history of recreational opioid use [101]. Each subject received single doses (separated by a 1-week washout period) of iv. placebo, 30 mg of iv. morphine alone, and 30 mg of iv. morphine in combination with 1.2 mg of iv. naltrexone. Subjects rated their response (over 24 h) using a visual analog scale in response to the question 'How high are you now?' The combination of morphine with naltrexone (to simulate parenteral use of crushed Embeda) resulted in a reduction in euphoria in 71% of subjects, when compared with morphine alone. Subjects response to the question 'How high are you now?' (Figure 3) was approximately 11-fold greater for morphine alone than for the combination of morphine plus naltrexone (to simulate tampered Embeda use). The Cole/Addiction Research Center Inventory (ARCI) euphoria response [18] was approximately two-fold greater for morphine alone than for morphine plus naltrexone (Figure 4). However, it is noteworthy that subjects did report some degree of euphoria compared with placebo.

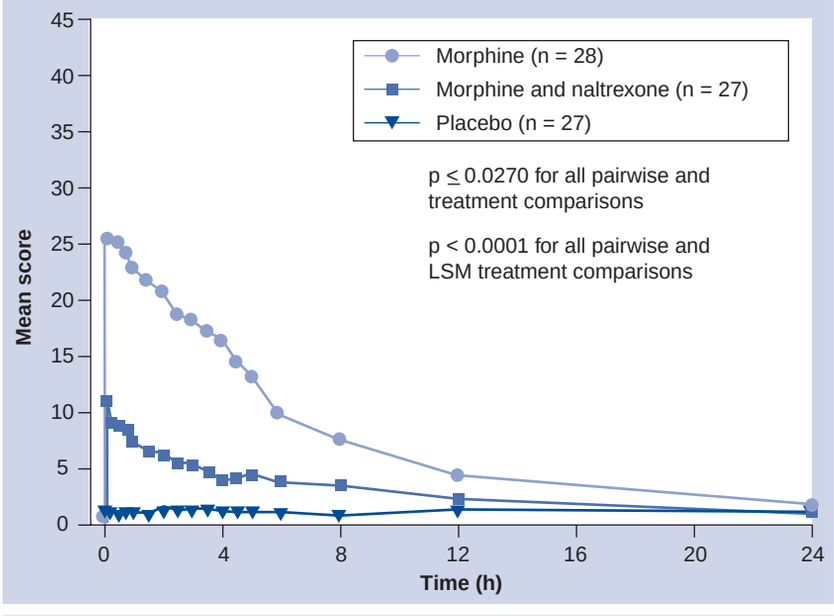

Figure 4. Mean subjective euphoria score is reduced among recreational opioid users with combination of intravenous naltrexone and intravenous morphine compared with intravenous morphine alone.
LSM: Least-squares means.
Data taken from [16].

Second, a study among 32 recreational opioid users aged 18–55 years compared pharmacodynamic responses after single doses of 120 mg of Embeda whole, 120 mg of Embeda crushed, 120 mg of immediate-release morphine solution and placebo using a randomized, double-blind, triple-dummy, four-way cross-over design with a minimum 2-week washout period [19]. Pharmacodynamic assessments included drug liking, feeling high, good effects and bad effects, all assessed using a visual analog scale, as well as ratings of euphoria and abuse potential. Scores for drug liking (Figure 5) were greatest for the oral morphine solution. Scores for feeling high and good effects were similar for Embeda crushed (55, 52) or Embeda whole (61, 59); and significantly higher for the morphine solution (90, 90) [16,19]. Administration of immediate-release morphine solution elicited a characteristic increase in scores for subjective positive effects compared with placebo. Compared with immediate-release morphine solution, treatment with Embeda whole and crushed resulted in a reduced response ($p < 0.01$) on measures of positive effects. It should be noted that although crushed Embeda released the dose of morphine immediately, rather than over a sustained period of approximately 12–24 h, tampering of the dosage form did not produce the significant increase in psychic effects expected from crushing a typical extended-release dosage form [16,101]. However, prescribing information for Embeda cautions that the clinical significance of this reduction in drug liking and euphoria has not yet been established [101]. Adverse events were more commonly reported with the morphine immediate-release solution compared with the Embeda capsule swallowed whole: euphoria (56 vs 28%) and pruritus (53 vs 28%) [19].

Clinical efficacy & safety

The clinical efficacy and safety of Embeda for the treatment of chronic pain has been evaluated in three clinical trials for patients with chronic nonmalignant pain. First, a 12-week double-blind, placebo-controlled, enriched enrollment, randomized, withdrawal clinical trial assessed the efficacy and safety of Embeda compared with placebo for the treatment of moderate-to-severe pain of osteoarthritis of the hip or knee [16,20,101]. This multicenter study enrolled 547 patients (mean age 55 years) with chronic pain and inadequate analgesia. Following a washout phase of up to 7 days, during which all analgesics were discontinued,

Embeda was titrated on an open-label basis to pain relief up to doses of 80 mg twice daily over a period of up to 6 weeks. Of note, 203 patients withdrew from the study during this titration period owing to opioid side effects, such as constipation and nausea. Most (75%) patients were opioid naive and this probably resulted in the significant drop-out rate. Once their pain was controlled (Brief Pain Inventory average 24-h pain intensity of 4 or less and at least a two-point drop from screening baseline), the remaining 344 patients were randomized and entered a 12-week double-blind maintenance phase during which they were maintained on Embeda or treated with placebo with a tapering dose of Embeda during the first 14 days. All patients were allowed acetaminophen as a rescue analgesic throughout the trial. The mean (standard deviation) pain intensity score at baseline (after washout from all analgesics) was 6.1 (1.9) and after the Embeda titration phase, it had decreased to 2.7 and 2.5 for the groups entering the Embeda or placebo maintenance phases. That is, as a group, patients completing the open-label titration phase with Embeda had excellent pain relief. During the 12-week maintenance phase, the mean change from randomization baseline to the end of the 12-week period was slightly better (minus 0.2) for the Embeda group compared with the placebo group (plus 0.3) (FIGURE 6). While this reduction in pain scores from the Embeda group compared with the placebo (with rescue acetaminophen) group is modest, it appears to be significant that the scores for patient physical function (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) were also better than the placebo group during this time period (FIGURE 7). However, it should be noted that the WOMAC differences of 4 mm between groups were compared on a scale of 0–100 scoring. Adverse events occurred principally during the titration period to mostly opioid-naive patients. During the maintenance phase, adverse events were mild (diarrhea: 12%; nausea: 12%) and similar for Embeda or placebo groups [20]. A self-reported measure of opioid-withdrawal scale did not show any significance, which suggests that the inner sequestered naltrexone did not leak out of the capsule.

Second, a clinical trial compared the efficacy of Embeda versus Kadian among 113 patients with moderate-to-severe chronic pain due to osteoarthritis [21]. Patients underwent an open-label titration on Kadian at a dose of up to 160 mg twice daily for up to 28 days, followed by randomization to a double-blind crossover treatment with Embeda or Kadian for 2 weeks. At the conclusion of 2 weeks of treatment, patients received 1 week of open-label Kadian, followed by crossover to the alternate double-blind treatment (Embeda or Kadian) for a further period of 2 weeks [21]. The mean numerical pain score at the beginning of the open-label titration was 7.1 and at randomization baseline it was 2.13, indicating that patients had been titrated to an effective dose for pain relief [16]. At the end of the 14-day treatment period, mean pain intensity scores were similar for Kadian (2.4) and Embeda (2.3) (FIGURE 8). The WOMAC Index for assessment of physical function was also similar for the two treatment medications. Adverse events (e.g., constipation, nausea and somnolence) were infrequent (8–15%) and similar between the two opioid formulations. The majority of patients rated both opioids as good to excellent.

Finally, a 2009 report of a 12-month, open-label safety study of Embeda for the treatment of chronic noncancer pain demonstrated that Embeda was generally safe and well tolerated during long-term opioid therapy [22]. Patients with chronic pain were eligible for the open-label 12-month study. Of the 467 patients who started the 1-year study, 465 patients received

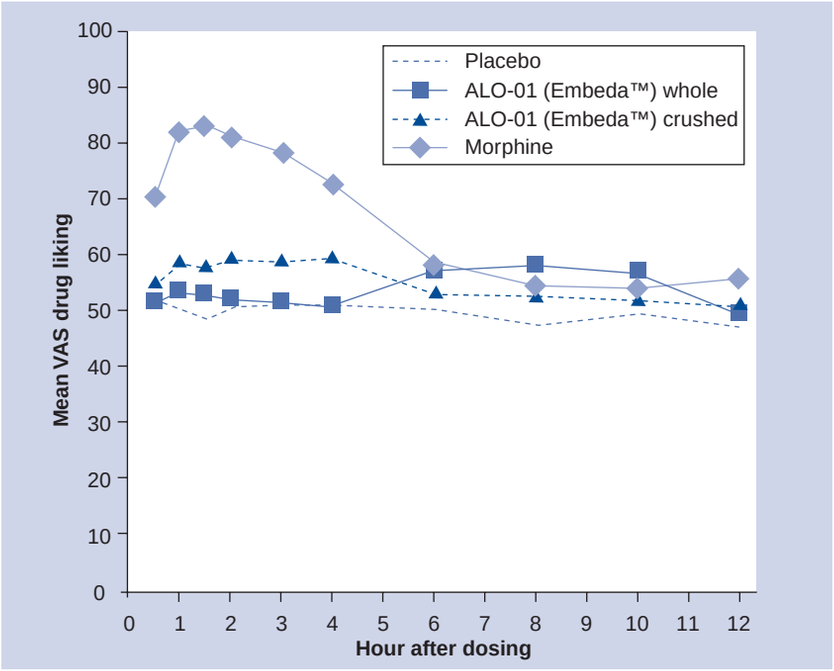

Figure 5. Mean visual analog scale drug-liking scores (0 = strong disliking; 100 = strong liking) among recreational drug users following single oral dose of medication is greatest for morphine solution.
VAS: Visual analog scale.
Data taken from [16].

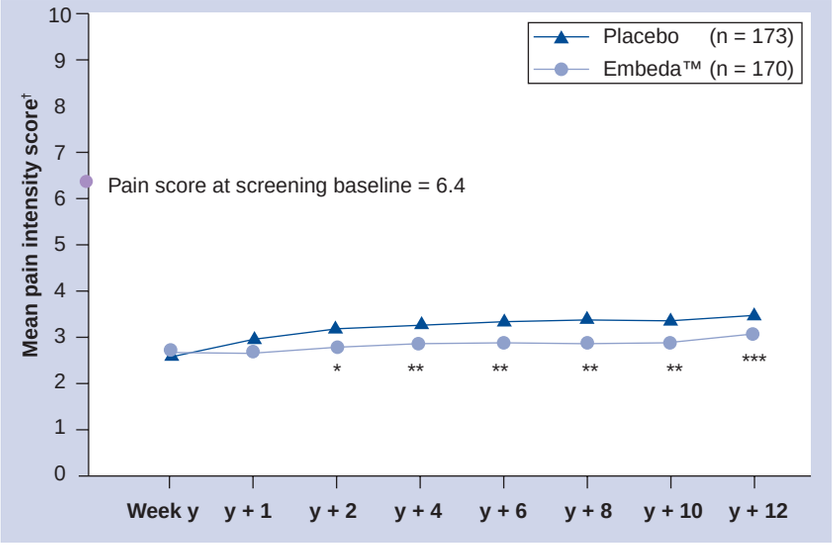

Figure 6. Mean pain intensity scores at baseline and throughout 12-week maintenance phase comparing Embeda™ versus placebo for the treatment of osteoarthritis pain.
*p = 0.006; **p = 0.0014; ***p = 0.0032.
†0: No pain; 10: worst possible pain.
Data taken from [16].

at least one dose, 208 patients received at least 6 months and 124 patients received 12 months of treatment with Embeda. Doses of Embeda (once or twice daily) were titrated upward to analgesia as required. A total of 299 patients received 80–120 mg/day, 79 patients received 80–120 mg/day and 78 patients received more than 120 mg/day of Embeda [22]. Embeda was found to be safe with adverse events mostly occurring during the first month of the titration phase, typical for the introduction of a patient to an opioid therapy. During the maintenance phase, common opioid side effects were reported: constipation (32%), nausea (25%), headache (12%) and vomiting (12%) [16]. Following the first month of the opioid titration, pain scores continued to decrease over time through week 28 and then remained stable through week 52, indicating maintenance of analgesia (Figure 9).

Clinical applicability

Embeda is a novel extended-release dosage form of morphine designed to reduce the risk of abuse, suitable for once- or twice-daily dosing and is bioequivalent to a well-established extended-release morphine (Kadian). It incorporates, in addition to morphine in extended-release form, naltrexone in a sequestered form. The naltrexone is nonreleasable when used as directed. However, when attempts are made to tamper with the dosage form in order to release the morphine for a rapid oral effect, or for nonoral use (e.g., iv. use), the naltrexone becomes released and thereby reduces or mitigates the effects of the morphine. Embeda is to be swallowed whole or the contents of the capsules sprinkled on applesauce. The pellets in the capsules are not to be crushed, dissolved or chewed.

Embeda has demonstrated clinical efficacy for chronic pain relief in patients with osteoarthritis of the hip or knee. However, in the only placebo-controlled clinical trial where Embeda was administered over 12 weeks, it provided modest (but statistically significant) differences from placebo (with rescue acetaminophen) in the primary end point of average pain score over 12 weeks (0.5 point difference on an 11-point Likert scale Brief Pain Inventory). This modest difference in pain relief in favor of Embeda may have been due in part to the use of a randomized withdrawal design in which all patients first received open-label Embeda for up to 6 weeks, thereby creating an expectation of effect in the placebo group. A 30% improvement has been reported as a clinically important difference in pain [23]. Using this criterion, the proportion of patients who experienced a 30% or less decrease in 24-h pain scores from screening baseline to week 12 of the maintenance phase was greater after Embeda treatment compared with placebo (mean difference 15%) [16].

The clinician would expect to use Embeda for patients with chronic nonmalignant pain from osteoarthritis who have not attained adequate pain relief with nonopioid analgesics.

Some clinical trials support the use of opioid analgesics in carefully selected patients with moderate-to-severe chronic pain who have attained suboptimal pain relief with nonopioid analgesics. However, it is often difficult to predict which patients will benefit from long-term opioid therapy. A recent review of available research data suggests that additional clinical trials are required on the long-term benefits and risks of chronic opioid therapy [24]. Some patients may experience inadequate pain relief in spite of escalating doses of opioids, while others may experience opioid-related side effects that limit their effectiveness [14].

Extended-release opioid analgesics, such as Embeda, are often used in the management of chronic pain since they are designed to maintain effective plasma levels throughout a 12- or 24-h dosing interval. This extended-release format has the potential to offer fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality-of-life outcomes, and increased control to patients

over the management of their pain. However, the extended-release formulations must necessarily contain a significant dose of opioid. Thus, tampering can rapidly deliver a dose of opioid that may produce life-threatening side effects. Several strategies have been suggested to deter the abuse of oral opioids including [1]:

- Opioid agonist formulation containing a sequestered opioid antagonist released upon tampering;
- Opioid agonist formulation with matrix to resist crushing, injection or solvent extraction;
- Opioid agonist formulation containing an unsequestered aversive agent (such as niacin) or a sequestered aversive agent (e.g., capsaicin) released upon tampering.

Embeda is designed as an opioid agonist formulation containing a sequestered opioid antagonist released upon tampering in order to help prevent the abuse and potential serious side effects associated with opioid use after product tampering. Whether this dosage form of morphine will result in fewer instances of prescription opioid abuse and serious side effects can only be determined following long-term use of the drug. A large, prospective epidemiology study will be required to determine if this novel opioid formulation does have a reduced risk of abuse.

There is a need for abuse-deterrent dosage forms of opioids, particularly extended-release opioids. Embeda is compatible with reduced risk of abuse when evaluated in nonopioid-dependent recreational drug users in the controlled setting of pharmacodynamic studies. It is reasonable to expect that it will also deter abuse in the 'real world' setting when the dosage form is tampered with to release the slow-release morphine (e.g., crushed or extracted with a solvent) and consumed by the oral or iv. routes of administration.

Conclusion

Embeda is an extended-release oral formulation of releasable morphine sulfate and sequestered naltrexone hydrochloride for the treatment of chronic pain. It is the first extended-release opioid formulated to help minimize the risk of abuse to be approved in the USA. The official US indication for Embeda and all other extended-release opioids is "for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time". Embeda is not intended for use as a *pro re nata* analgesic or for the treatment of acute pain. Embeda is designed to help reduce abuse risk by blunting the effects of morphine when the dosage form is tampered with. As with all other opioid analgesics, Embeda provides an opioid effect when taken intact. As such, it can be abused when taken intact and it may not reduce the risk of iatrogenic addiction to opioids. Therefore, careful patient selection and rigorous monitoring continue to remain important aspects of its use. Nonetheless, the introduction of Embeda represents a major advance in the field of abuse-deterrent opioid analgesics.

Future perspective

A concern of clinicians using opioid analgesics for the treatment of chronic noncancer pain is the risk of willful abuse. Although the majority of patients receiving an opioid for the medically indicated treatment of chronic pain will not abuse it, there is considerable diversion of opioids for nonmedical use by recreational drug users and by opioid-dependent individuals with an addiction disorder. Perhaps most tragically, the nonmedical use of opioids has the effect of reducing the availability of an important treatment option to patients with chronic pain. Many clinicians become reticent to prescribe opioids owing to concerns about potential misuse or diversion of the drug. Embeda is an oral formulation of morphine that is designed to help reduce the abuse of prescription opioids.

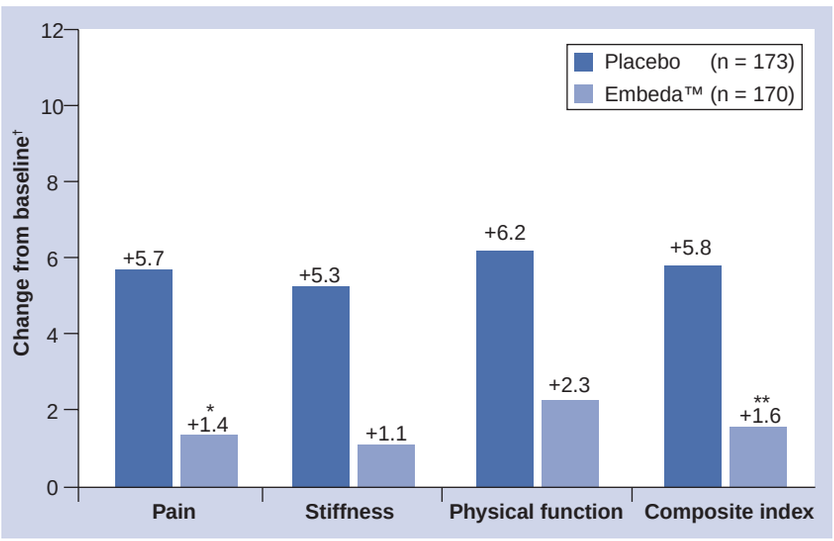

Figure 7. Mean change from baseline on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) throughout the 12-week maintenance phase comparing Embeda™ versus placebo for the treatment of osteoarthritis pain.
*p = 0.0229; **p = 0.0312.
†Randomization baseline (week Y).
Data taken from [16].

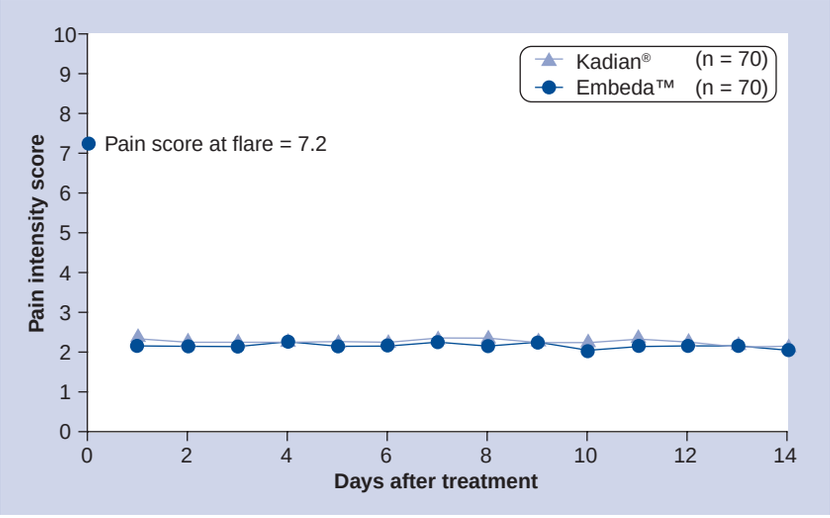

Figure 8. Mean daily average pain intensity score after Embeda™ and Kadian® in patients with moderate-to-severe pain of osteoarthritis of the hip or knee. Pain intensity score: 0: no pain; 10: worst possible pain.
Data taken from [16].

A wide variety of technologies have been described to deter the abuse of opioids. The use of sequestered opioid antagonists that become releasable upon tampering (e.g., crushing or solvent extraction), as is the case with Embeda, is one such approach. Other aversive agents in sequestered form (e.g., bittering agents, pungent agents and emetics) have also been described. Since a major concern with the abuse of extended-release opioids is the physical manipulation of the dosage form to defeat the controlled-release mechanism and make the entire content immediate release, alternative abuse-deterrent formulations in development include technologies that deter the crushing, powdering, melting and chemical extraction of the dosage form in order to frustrate or resist oral ingestion in immediate-release form, inhalation, insufflation and iv. injection. If prior drug development history is any guide, such abuse-deterrent strategies will probably be apparent only through postmarketing surveillance of several formulations with competing technologies. In addition, there exist considerable regional differences in patterns of abuse, which means that different abuse-deterrence strategies may be required in different areas of the world. The experience with substance abusers indicates that habitual abusers, with ready access to information from websites on how to optimally extract the active agent, are frequently only one step behind strategies to deter abuse. Therefore, the development of abuse-deterrent formulations has become a major pharmaceutical, clinical, regulatory and law enforcement challenge [25]. Embeda is the first approved opioid formulation designed to help minimize prescription drug misuse, but there will be many other such drug formulations released in the next few years.

There is, therefore, a continued need for pharmaceutical research to formulate opioids with a robust extended-release pharmacokinetic profile suitable for once- or twice-daily oral dosing, but also containing abuse deterrence properties. There is also a need for pharmaceutical research and development on extended-release formulations of opioids that are stable (i.e., do not dose dump) when used at therapeutic doses in conjunction with alcohol. An ideal opioid oral formulation will provide an extended-release pharmacokinetic profile suitable for 12- to 24-h release, will be resistant to crushing at room temperature, and resistant to extraction (upon freezing/melting) with recreational solvents, all without doing harm to patients. New opioid formulations will require large prospective epidemiology studies to determine if a formulation has a reduced risk for abuse.

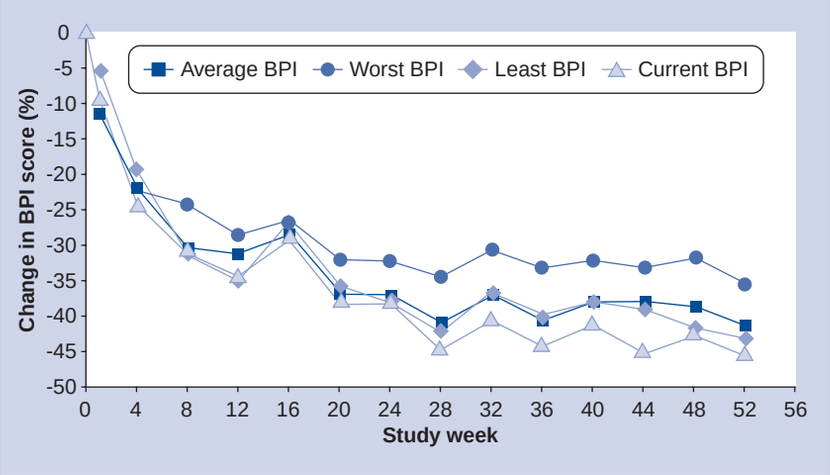

Figure 9. Percent change in Brief Pain Inventory pain scores throughout a 52-week follow-up of patients taking Embeda™ for chronic nonmalignant pain.
BPI: Brief Pain Inventory.
Data taken from [16].

Financial & competing interests disclosure

Najib Babul works at TheraQuest, a pharmaceutical company involved in the development of opioid and nonopioid analgesics for acute and chronic pain. He has consulted with a variety of pharmaceutical companies involved with the development of analgesics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Chemistry

- Embeda™ is an extended-release (once or twice daily) oral formulation of releasable morphine sulphate and sequestered naltrexone for the treatment of chronic pain.
- Embeda pellets combine morphine, surrounded by an extended-release coating, with an inner, sequestered core of naltrexone (opioid antagonist).
- When taken as directed, the sequestered naltrexone is not released, and Embeda is bioequivalent to the extended-release morphine Kadian®.
- If Embeda is crushed (as in misuse), the naltrexone is released and antagonizes the effect of morphine.

Pharmacokinetics

- Embeda is bioequivalent to Kadian and administered with once- or twice-daily dosing.
- Time to peak plasma morphine concentration is 7.5 h.
- Morphine bioavailability is minimally influenced by food.
- Morphine is cleared principally by the liver.
- Pharmacokinetics of the opioid antagonist, naltrexone, are very dependent on whether the capsule is taken as directed (whole) or crushed (abused). When taken whole naltrexone is not appreciably absorbed. When taken crushed, naltrexone is completely absorbed as after oral immediate-release naltrexone.

Pharmacodynamics

- Embeda taken in a crushed form resulted in a much reduced 'positive liking' of the effect compared with immediate-release morphine. This is the essential basis for the deterrent aim of Embeda.

Clinical efficacy

- Two double-blind, randomized clinical trials demonstrate analgesia and improved physical functioning with the use of Embeda for the treatment of chronic osteoarthritis pain.
- Adverse side effects of Embeda are infrequent and similar to current opioid formulations.

Clinical application

- Embeda is the first morphine formulation approved with a dosage format that aims to deter opioid misuse from crushing or chewing the product. Long-term follow-up is required to verify if this deterrent effect will be sustained.

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