Future of minimizing opioid adverse effects while maintaining or improving opioid-related analgesia

Opioids are potent broad-spectrum analgesics that may provide significant relief from severe pain and suffering. However, unfortunately, opioids possess certain qualities and adverse effects that may detract from their potential benefits or even contribute to patients discontinuing chronic opioid therapy despite obtaining significant opioid-induced analgesia. Opioid-induced adverse effects represent a significant obstacle in achieving appropriate analgesia and/or patient comfort. Investigators continue major efforts to develop novel opioids and other analgesics and strategies, as well as efforts to improve existing analgesics such as opioids. Multiple efforts to modify opioid analgesic agents aiming to improve analgesia and/or minimize unwanted effects are ongoing. These strategies include the development of combination opioid analgesics, 'alternative opioids' and peripherally acting opioids.

KEYWORDS: adverse effects ■ minimizing ■ nausea ■ opioid ■ opioid-induced hyperalgesia ■ pain ■ tolerance ■ vomiting

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Currently, no ideal analgesic exists. Characteristics of an 'ideal' analgesic may include:

- The agent being a full agonist providing optimal/maximal analgesia for a wide range/variety of pain states (e.g., broad-spectrum analgesic activity);
- The agent not exhibiting tolerance;
- Not producing unwanted effects and minimal adverse effects;
- The agent having no addictive potential;
- Not facilitating pain/hyperalgesia;
- The agent having a long duration;
- High oral bioavailability;
- The agent not being vulnerable to important drug interactions;
- Not being significantly bound to plasma proteins;
- The agent having no active metabolites;
- The agent having linear kinetics;
- The agent being eliminated partly by hydrolysis to an inactive metabolite (without involvement of oxidative and conjugative enzymes).

Opioids are potent broad-spectrum analgesics that may provide significant pain relief, but are not 'ideal' and may be associated with a variety of unwanted effects.

Opioid-induced adverse effects (OIAEs) represent a significant problem in efforts to alleviate pain and achieve patient comfort. Patients experiencing significant opioid-induced adverse effects will likely be unable to tolerate aggressive titration schedules to higher opioid doses at which they may achieve analgesia. Furthermore, even if patients achieve adequate analgesia at high opioid doses, along with concomitant persistent opioid-induced adverse effects, some patients may decide to abandon chronic opioid therapy (COT), deciding that they would rather suffer 'and put-up' with significant pain than to experience the OIAEs.

Kalso *et al.* analyzed available randomized, placebo-controlled trials of WHO step 3 opioids for efficacy and safety in chronic noncancer pain, evaluating eleven studies (1025 patients) that compared oral opioids with placebo for 4 days to 8 weeks [1]. Approximately 80% of patients experienced at least one adverse event, with constipation (41%), nausea (32%) and somnolence (295), vomiting (15%) and itching (15%) being the most common. Only 44% of 338 patients on open-label treatments were still on opioids after therapy for between 7 and 24 months [1].

Opioid-induced adverse effects have also been frequently reported for patients with neuropathic pain [2], cancer pain [3] and postoperative pain [4]. Kwong *et al.* found that most patients treated with schedule II and III immediate-release oral opioids experienced OIAEs and desired improvement of these effects, with

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constipation, nausea and somnolence being the most frequently reported [5]. In a survey of patients using adaptive conjoint analysis, they reported that reducing the risk of experiencing OIAEs was of sufficient importance for patients to be willing to give up a degree of adequate and satisfactory pain relief [5]. The trade-offs that they were willing to make were greatest for nausea and vomiting, followed by itching and constipation [5].

Assessment of OIAEs

Although there are multiple ways to assess commonly experienced OIAEs in COT, a qualitative assessment is included in the Pain Assessment and Documentation Tool [6,7], and a quantitative assessment that can be followed for trends longitudinally is the Numerical Opioid Side Effect (NOSE) tool [8] (Table 1).

Minimizing opioid adverse effects

Ten potential strategies that may ameliorate many OIAEs include:

- 1. Decreasing the dose of opioids, or in some cases reducing the dramatic peaks and troughs from short-acting opioid therapy, changing to a controlled-release formulation leading to a relatively constant serum level (for a review of enteral controlled release opioids, see [9]);
- 2. Discontinuing opioid therapy;
- 3. Adding nonpharmacologic therapies, nonopioid analgesics and/or various co-analgesics or 'adjuvant analgesics' in efforts to decrease or discontinue opioids;
- 4. Switching to a different opioid (e.g., opioid rotation) [10,11] or utilizing other strategies to reduce adverse effects by attempting to inhibit the generation, enhance the metabolism or diminish the functionality of active opioid metabolites, since some adverse effects may occur, in part, from active metabolites;
- 5. The use of 'ultra-low-dose', low-dose opioid antagonists or peripherally restricted opioid antagonists, along with opioid agonists;
- 6. The use of specific therapeutic measures to address individual adverse effects;
- 7. The use of alternative routes of administration (e.g., intrathecal) [12,13] (the use of systems which provide the optimal concentrations of opioid analgesics to their optimal targets);
- 8. The use of additional agents that either minimize the occurrence/frequency/severity of OIAEs or potentiate opioid analgesia (e.g., provide analgesic synergy) so that the dose of opioid required for the same level of analgesia is reduced (e.g., combination opioid analgesics [COAs]) [14];
- 9. The use of 'alternative opioid analgesics' having nontraditional functional interactions with various opioid receptors (e.g., selective δ-opioid receptor agonists) or 'atypical opioids' having opioid properties/characteristics as well as nonopioid properties/characterisitics (e.g., μ-opioid receptor agonist/noradrenergic modulators [MORANAMs], e.g., tapentadol);
- 10. The use of peripheral acting opioids (PAOs) [15].

Sometimes it may be beneficial to combine two or more of these strategies in attempts to overcome OIAEs (e.g., the use of all routes of administration [intrathecal morphine] combined with the use of nonopioid analgesics [ziconotide]). Strategies 1 through 7 are reasonably traditional

Table 1. Numerical opioid side effect (NOSE) assessment tool.

Side effects	Not present										As bad as you can imagine
Nausea, vomiting and/or lack of appetite	0	1	2	3	4	5	6	7	8	9	10
Fatigue, sleepiness, trouble concentrating, hallucinations and/or drowsiness/somnolence	0	1	2	3	4	5	6	7	8	9	10
Constipation	0	1	2	3	4	5	6	7	8	9	10
Itching	0	1	2	3	4	5	6	7	8	9	10
Decreased sexual desire/function and/or diminished libido	0	1	2	3	4	5	6	7	8	9	10
Dry mouth	0	1	2	3	4	5	6	7	8	9	10
Abdominal pain, discomfort, cramping or bloating	0	1	2	3	4	5	6	7	8	9	10
Sweating	0	1	2	3	4	5	6	7	8	9	10
Headache and/or dizziness	0	1	2	3	4	5	6	7	8	9	10
Urinary retention	0	1	2	3	4	5	6	7	8	9	10

Data from [8].

and familiar to many clinicians at this point in time, so the following sections will explore strategies 8 through 10. However, before focusing on strategies 8 through 10, strategy 5 will be further explored.

Opioid agonists & 'ultra-low-dose' opioid antagonists

Crain and Shen discovered basic scientific evidence that theoretically supported the concept of adding an ultra-low-dose of an opioid antagonist to an opioid agonist in efforts to diminish opioid-induced adverse effects and potentially enhance analgesia [16]. However, initial attempts to add agents such as naloxone to morphine were not met with success. Despite this, ongoing investigative efforts involving opioid agonist/opioid antagonist combinations continue.

Chindalore *et al.* conducted a 3-week, Phase II clinical trial that assessed the safety and analgesic efficacy of Oxytrex™ (a drug that combines oxycodone with ultra-low-dose naltrexone) in patients with moderate-to-severe pain from osteoarthritis [17]. Patients were randomized to receive placebo, oxycodone four-times a day (q.i.d.), Oxytrex q.i.d., or Oxytrex twice a day (b.i.d.). All active treatment groups received the same total daily dose and dose escalation of oxycodone, starting at 10 and ending at 40 mg/day. The Oxytrex b.i.d. group received a lower daily dose of naltrexone than Oxytrex q.i.d. (0.002 vs 0.004 mg/day). Oxytrex b.i.d. produced a 39% reduction in pain intensity, which was significantly greater than that of placebo ($p < 0.0001$), oxycodone q.i.d. ($p = 0.006$), and Oxytrex q.i.d. ($p = 0.003$) [17]. Oxytrex b.i.d. was also superior to placebo in quality of analgesia ($p = 0.002$), duration of pain control each day ($p = 0.05$), patients' global assessments ($p = 0.04$), and the Western Ontario and MacMaster Universities Osteoarthritis Index total score ($p = 0.03$) [17]. The incidence of side effects was comparable between active treatments [17].

Researchers continue to evaluate combination agents with opioid agonists and opioid antagonists with respect to improving gastrointestinal transit time in patients requiring opioids. Oxycodone/naloxone (2:1 ratio) prolonged release (PR) was compared with oxycodone PR alone over a 12-week period, and a comparable analgesia but a significant improvement in bowel function in those taking the oxycodone/naloxone combination ($p < 0.001$) was demonstrated [18,19].

Imasogie and colleagues performed a pilot study with ten patients 70 years of age or older undergoing either total knee (n = 7) or total hip (n = 3) arthroplasty who were treated prospectively [20]. Each patient received two tablets of tramadol/acetaminophen (Tramacet®; Janssen-Ortho Inc., ON, Canada) preoperatively and every 6 h post-operatively, as well as a naloxone infusion started preoperatively at 0.25 µg/kg/h and continued up to 48 h post-operatively [20]. Post-operative opioid use was reduced by 80% compared with historic controls [20].

Peripherally-restricted opioid antagonists

A strategy designed especially to diminish opioid-induced gastrointestinal delayed transit time or opioid-induced constipation is the use of peripherally-restricted opioid antagonists. Two such agents that address this unwanted effect are methylnaltrexone and alvimopan, which are US FDA approved for two different indications.

Methylnaltrexone is a quaternary opioid antagonist that crosses the blood–brain barrier very poorly compared with tertiary compounds due to its greater polarity and resultant lipophobic nature [21]. Methylnaltrexone bromide is FDA-approved as a subcutaneous injection (12 mg/0.6 ml per vial) for opioid-induced constipation in patients with advanced illness receiving palliative care after failing laxative therapy. The patient can be given one weight-based dose every other day as needed, with a maximum daily dose of one dose in a 24-h period (**Table 2**) [21]. Methylnaltrexone has an onset of action that is usually approximately 30–60 min, protein binding of 11–15%, and terminal elimination half-life of approximately 8 h [21]. It is metabolized to methyl-6-naltrexol isomers, methylnaltrexone sulfate and other minor metabolites [21].

Table 2. Methylnaltrexone dosing.

Patient characteristic	Dose
Weight <38 kg	0.15 mg/kg/dose (calculate injection volume [weight in kg × 0.0075] and round to the nearest 0.1 ml)
Weight 38 to <62 kg	8 mg/dose (0.4 ml)
Weight 62 to 114 kg	12 mg/dose (0.6 ml)
Weight > 114 kg	0.15 mg/kg/dose (calculate injection volume [weight in kg × 0.0075] and round to the nearest 0.1 ml)
Renal impairment (creatinine clearance < 30 ml/min)	Reduce dose by one-half

Yuan *et al.* studied 22 subjects enrolled in a methadone maintenance program with a randomized placebo-controlled trial [22]. All subjects who received methylnaltrexone (intravenous) experienced laxation without opioid withdrawal or significant side effects [22].

Thomas *et al.* conducted a randomized placebo-controlled study of 0.15 mg/kg methylnaltrexone subcutaneous versus placebo every other day for 2 weeks in patients with advanced illness [23]. A total of 48% of patients receiving methylnaltrexone experienced rescue-free laxation within the first 4 h after the first dose, compared with 15% who received placebo ($p < 0.001$) [23]. Over the course of the first four doses, the proportion of patients having a rescue-free laxation within 4 h ranged from 38 to 48% in patients administered methylnaltrexone, and 7–15% in those given placebo. Approximately half of patients who experienced rescue-free laxation within 4 h had a response within 30 min. There were no differences in pain scores between the methylnaltrexone and placebo groups, and there was no evidence of significant opioid withdrawal.

Portenoy and colleagues performed a randomized, parallel-group, repeated dose, dose-ranging trial (1, 5, 12.5 and 20 mg) that included a double-blind phase for 1 week, followed by an open-label phase for a maximum of 3 weeks, and found that methylnaltrexone relieved opioid-induced constipation at doses ≥5 mg in patients with advanced illness, and did not detract from analgesia or cause opioid withdrawal symptoms [24].

Slatkin *et al.* studied 154 patients with advanced illness receiving a single dose of 0.15 or 0.3 mg/kg subcutaneous methylnaltrexone or placebo, and demonstrated that 58–62% of patients experienced laxation within 4 h of dose administration [25]. Yuan *et al.* have investigated an enteric-coated oral formulation of methylnaltrexone in a randomized, controlled study, which appears to be as efficacious as the parenteral form [22] and likely has a direct local bowel action [26].

Alvimopan is a large oral peripherally restricted opioid antagonist that is metabolized in the gut (systemic absorption in humans may be up to 6%) and is indicated to accelerate the time to upper and lower gastrointestinal recovery following surgery with primary anastomosis. Dosing for the management of post-operative ileus is an initial 12 mg administered orally 30 min to 5 h prior to surgery, with a maintenance of 12 mg twice daily beginning the day after surgery for a maximum of 7 days or until discharged from hospital (maximum total treatment doses: 15 doses). Alvimopan has been shown to be efficacious with respect to reducing post-operative ileus after surgery [27,28].

Although there is no FDA-approved indication, Webster *et al.* evaluated alvimopan in 522 patients receiving opioids for chronic noncancer pain [29]. Alvimopan was associated with an increase in the number of spontaneous bowel movements compared with placebo ($p < 0.001$) [29].

Combination opioid analgesics

The addition of an analgesic with a second agent (that may or may not also be an analgesic) to achieve a 'combination analgesic' is a concept that has been exploited for many years. Reasons for combining an opioid with a second agent to produce a COA may include:

- Combinations to prolong analgesic duration;
- Combinations to enhance or optimize analgesic efficacy (e.g., analgesic synergy);
- Combinations to diminish or minimize adverse effects;
- Combinations to diminish opioid effects that are not beneficial (or contrariwise to or enhance beneficial opioid effects);
- Combinations to reduce opioid tolerance/opioid-induced hyperalgesia (OIH);
- Combinations to combat dependency issues/addiction potential/craving sensations [14].

Gilron *et al.* compared the efficacy of a combination of gabapentin and morphine with that of each as a single agent in patients with painful diabetic neuropathy or postherpetic neuralgia [30] in a randomized, double-blind, active placebo-controlled, four-period crossover trial. Patients received daily active placebo (lorazepam), sustained-release morphine, gabapentin and a combination of gabapentin and morphine – each given orally for 5 weeks. The primary outcome measure was mean daily pain intensity in patients receiving a maximal tolerated dose; secondary outcomes included pain (rated according to the Short-Form McGill Pain Questionnaire), adverse effects, maximal tolerated doses, mood and quality of life. Total scores on the Short- Form McGill Pain Questionnaire (on a scale from 0 to 45, with higher numbers indicating more severe pain) at a maximal tolerated dose were 14.4 with placebo, 10.7 with gabapentin, 10.7 with morphine and 7.5 with the gabapentin–morphine combination. The maximal tolerated doses of morphine and gabapentin were lower with the combination than for each drug as a single agent [30].

In efforts to enhance opioid analgesic efficacy, Tai *et al.* performed a study to evaluate the effects of the tricyclic antidepressant amitriptyline on morphine tolerance in rats [31]. Morphine induced antinociceptive tolerance and downregulation of spinal glutamate transporters (GLAST, GLT-1 and EAAC1) in the rat spinal cord dorsal horn (DH). Coadministration of amitriptyline with morphine attenuated morphine tolerance and upregulated GLAST and GLT-1 expression [31]. On day 5, morphine challenge (10 μg/10 μl) resulted in a significant increase in levels of excitatory amino acids, aspartate, and glutamate in cerebrospinal fluid dialysates in morphine-tolerant rats. Amitriptyline coinfusion not only markedly suppressed this morphine-evoked excitatory amino acid release, but also preserved the antinociceptive effect of acute morphine challenge at the end of infusion [31]. The activation of glial cells and increased cytokine expression (TNF-α, IL-1β and IL-6) in the rat spinal cord were induced by the 5-day morphine infusion, and these neuroimmune responses were also prevented by amitriptyline co-infusion [31]. Their results show that amitriptyline not only attenuates morphine tolerance, but also preserves its antinociceptive effect. The mechanisms involved may include inhibition of proinflammatory cytokine expression, prevention of glutamate transporter downregulation, and even upregulation of spinal glial GLAST and GLT-1 expression, with attenuation of morphine-evoked excitatory amino acid release following continuous long-term morphine infusion [31].

Fairbanks and Wilcox demonstrated that spinal antinociceptive synergism between morphine and clonidine persists in mice made acutely or chronically tolerant to morphine [32]. In all morphine pretreated groups, the combination of morphine and clonidine resulted in significant leftward shifts in the dose-response curves compared with those of each agonist administered separately [32]. In all tolerant and control groups, the combination of morphine and clonidine produced a significantly lower ED_{50} value than the corresponding theoretical additive ED_{50} value [32]. Morphine and clonidine synergized in morphine-tolerant as well as in control mice. Fairbanks and Wilcox suggested that spinally administered adrenergic/opioid synergistic combinations may be effective therapeutic strategies to manage pain in patients apparently tolerant to the analgesic effects of morphine [32].

Tramadol, a centrally acting analgesic structurally related to codeine, is a racemate that weakly binds to the μ-opioid receptors (MORs), producing some analgesia, and also inhibits the reuptake of norepinephrine and serotonin, which produces the majority of its analgesia. It is conceivable that the interaction of MOR agonists with inhibitors of norepinephrine reuptake may lead to improved analgesia, and one agent, tapentadol, possesses both of these characteristics. Although tapentadol exhibits weak interactions at both MORs and norepinephrine transporters, it possesses strong analgesic activity on par with that of oxycodone, but with less gastrointestinal adverse effects (e.g., nausea, vomiting and constipation). If an analgesic interaction between norepinephrine and opioids is found to yield improved analgesia, then perhaps a norepinephrine reuptake inhibitor (e.g., reboxetine) with an opioid may be a reasonable COA to pilot.

Cox *et al.* revealed that isobolographic analyses indicated a synergistic interaction between Δ(9)-tetrahydrocannabinol (THC) and morphine in both nonarthritic and arthritic rats [33]. Smith *et al.* demonstrated that low-dose THC–morphine combination treatment produces antinociception in the absence of tolerance or attenuation of receptor activity [34]. Narang *et al.* assessed the efficacy of dronabinol (Marinol® capsules, Solvay Pharmaceuticals, Brussels, Belgium), a synthetic Δ9-THC, in 30 patients taking opioids for chronic pain to determine its potential analgesic effects as an adjuvant treatment [35]. Phase I of this two-phase study was a randomized, single-dose, double-blinded, placebo-controlled, crossover trial in which subjects were randomly administered either 10 mg or 20 mg of dronabinol or identical placebo capsules over the course of three 8-h visits [35]. Results of the Phase I study demonstrated that patients who received dronabinol experienced decreased pain intensity and increased satisfaction compared with placebo [35]. In the Phase II trial, titrated dronabinol contributed to significant relief of pain, reduced pain bothersomeness, and increased satisfaction compared with baseline. The incidence of adverse effects was dose related. Overall, the use of dronabinol was found to result in additional analgesia among patients taking opioids for chronic noncancer pain.

Baclofen, a GABA B agonist, may be potentially useful in patients with substance use disorders/dependency issues. Baclofen (Lioresal®) has been shown in laboratory animals to modulate cocaine self-administration, as well as reduction of response behaviors [36]. Baclofen may also show similar effects in humans, effects that are also dependent upon pattern as well as level of cocaine exposure [37]. The coadministration

of muscimol or baclofen increased the antinociceptive effects of morphine in intensity and duration [38]. L-baclofen may possess even greater antinociceptive properties, potentially yielding improved analgesia for trigeminal neuralgia versus racemic baclofen [39]. Furthermore, preclinical data in rats have revealed that when baclofen was coadministered with morphine or fentanyl, baclofen exhibited additive nociceptive effects and significantly suppressed retching and vomiting induced by morphine, as well as inhibited place preference elicited by morphine or fentanyl [40]. Baclofen may have a place in the therapeutic armamentarium for pain and chemical dependency, and have potential for future combination products, since it may be useful in providing analgesic synergy, diminishing OIAEs, and potentially providing beneficial effects with opioid-dependency issues [41]. Thus, morphine and baclofen ('morphlofen') may be of interest.

Morphine upregulates functional expression of the NK-1 receptor (NK-1R) in cortical neurons (as evidenced by mRNA levels, as well as immunofluorescence and western blot assays using specific antibody to NK-1R protein), possibly via MOR-induced changes in cyclic adenosine monophosphate, leading to activation of the p38 MAPK signaling pathway (via phosphorylation) and activation of the NK-1R promoter [42]. Therefore, it does not seem unreasonable that aprepitant – an NK-1R antagonist used for the treatment of post-operative nausea and vomiting and chemotherapy-induced nausea/vomiting, CINV – may be effective in treating opioid-induced nausea and vomiting (OINV). 'Aprepioid', a hypothetical COA of aprepitant and an opioid, may be an interesting combination product.

Prolonged opioid exposure enhances a descending pain faciliatory pathway from the rostral ventromedial medulla that is mediated at least in part by CCK activity and contributes to the maintenance of antinociceptive tolerance [43].

Furthermore, downstream from this, in the DH of the spinal cord, 5-HT3 receptors may be involved in distal aspects of this descending pain facilitatory pathway, which inputs into NK-1 expressing DH cells [44]. Thus, intrathecal (IT) 5-HT3 receptor antagonists or IT NK-1 antagonists may be beneficial for future therapeutic options if proved to be safe intrathecally for use in conjunction with long-term opioid therapy. CCK antagonists may not only be useful in opioid-induced antinociceptive tolerance, but perhaps may also have a beneficial role in attenuating opioid-induced drug craving [45].

IT 5-HT-3 receptor antagonists [46] and IT NK-1 antagonists may interfere with the function of NK-1 cells in the DH of the spinal cord (which normally promotes descending facilitatory pathways).

Morphine-induced hyperalgesia was reversed by spinal administration of an NK-1 receptor antagonist in rats and mice, and was observed in wild-type (NK-1[$^{+/+}$]), but not NK-1 receptor knockout (NK-1[$^{-/-}$]), mice [45]. Spinal NK-1 receptor-expressing neurons appear to contribute to mediating OIH and antinociceptive tolerance via activation of descending facilitatory pathways [47,48].

McNaull *et al.* administered three IT injections of morphine (15 µg) in adult rate, at 90-min intervals, and produced a significant decline of the antinociceptive effect and loss of agonist potency in both the tail-flick and paw-pressure tests [49]. These reduced responses, indicative of acute tolerance, were blocked by coinjection of morphine (15 µg) with naltrexone (0.05 ng), D-Phe-Cys-Try-D-Orn-Thr-Pen-Thr-NH_2 (CTAP, 0.001 ng), naltrindole (0.06 ng) or nor-binaltorphimine (0.1 ng) [49].

The sustained antinociception produced by combination of morphine with an opioid receptor antagonist may be related to dependency on adenosine receptor activity [49]. Combined µ-opioid receptor agonist adenosine receptor modulators (MORAARMs) may be worthwhile investigating.

Glial cells have been shown to contribute to and/ or facilitate various pain states [50] and may contribute to opioid tolerance, addiction and/or adverse effects. Opioids such as morphine can diminish pain but may also activate glial cells (likely via agonist activity at the toll-like receptor 4 [TLR4]), which may be counterproductive in terms of analgesia [51].

Ibudilast (AV-411), a nonselective phosphodiesterase inhibitor known to suppress glial cell activation, appears to essentially block morphine's direct effects on glia but not on neurons [52]. Rats injected with both AV411 and morphine exhibited increased analgesia, as well as less tolerance (i.e., over time morphine better retained its analgesia) compared with rats injected with morphine alone [52].

Systemic co-administration of minocycline significantly attenuated morphine-induced reductions in tidal volume, minute volume, inspiratory force and expiratory force, but did not affect morphine-induced reductions in respiratory rate. Minocycline attenuation of respiratory depression was also paralleled with significant attenuation by minocycline of morphine-induced reductions in

blood oxygen saturation. Minocycline also attenuated morphine-conditioned place preference [53]. Morphine analgesia was significantly potentiated by minocycline co-administration [53].

Yao *et al.* found that an adenosine A2a receptor administered either directly into the nucleus accumbens or indirectly by intraperitoneal injection eliminates heroin-induced reinstatement in rats trained to self-administer heroin, a model of human craving and relapse, and suggested that A2a antagonists might be effective therapeutic agents in the management of heroin withdrawal [54].

Repeated administration of morphine in rodents promotes the nitration, and thus the enzymatic inactivation, of spinal manganese superoxide dismutase [55]. Consequently, morphine may provide a key source of spinal peroxynitrite that contributes to the development of morphine antinociceptive tolerance through three well-defined biochemical pathways within the DH of the spinal cord: post-translational nitration of proteins involved in glutamate homeostasis neuroimmune activation (release of pro-inflammatory cytokines such as TNF-α, IL-1b and IL-6) and neuronal apoptosis [55,56]. Thus, reducing ONOO- formation either indirectly (with nitric oxide synthase inhibitors or superoxide dismutase inhibitors) or directly (using pharmacological approaches to catalytically decompose ONOO-) inhibits these three events [55,56].

It appears that 'upstream' synthesis of spinal ceramide may lead to peroxynitrite generation with repeated morphine administration, with consequent resultant antinociceptive tolerance.

In a murine model of opioid antinociceptive tolerance, repeated administration of morphine significantly stimulated the enzymatic activities of spinal cord serine palmitoyltransferase, ceramide synthase and acid sphingomyelinase (enzymes involved in the *de novo* and sphingomyelinase pathways of ceramide biosynthesis, respectively) and led to peroxynitrite-derive nitroxidative stress and neuroimmune activation (activation of spinal glial cells and increase formation of TNF-α, IL-1β and IL-6) [57]. Inhibition of ceramide biosynthesis with various pharmacological inhibitors significantly attenuated the increase in spinal ceramide production, nitroxidative stress and neuroimmune activation with resultant inhibition of morphine antinociception tolerance [57].

Alternative opioids

δ-opioid receptor agonists

Potent and selective δ-opioid agonists based on the pyrrolomorphinan framework have been designed, synthesized and characterized biologically [58]. In animal models, a selected compound of interest, SB 235863, has supported the notion that selective δ-opioid agonists may have potential as analgesic agents in inflammatory and neuropathic pain conditions, and with minimal OIAEs usually associated with the use of μ-opioid receptor agonists (e.g., morphine).

Multiple δ-selective agonists have demonstrated efficacy in various animal models of pain [59–63]. In addition, these agents may possess potential clinical benefits compared with the μ-agonists currently used for pain relief, including reduced respiratory depression [64], constipation [61], physical dependence [65] and abuse liability [64].

Compound 20, a potent and highly selective full agonist at the δ-opioid receptor that is structurally distinct from other chemical classes of δ-agonists, was studied in normal healthy volunteers, where it was found to be well tolerated with good oral exposure and a pharmacokinetic profile that may be suitable for once- or twice-daily dosing [66].

κ-opioid receptor agonists

κ-opioid receptor (KOR) agonists produce antinociceptive effects through interaction with peripheral KOR in inflammatory pain models [67,68] and in thermal hyperalgesia induced by capsaicin [69]. KOR agonists not only have analgesic activity, but also exhibit anti-inflammatory activity [68]. Because of the activity of KOR agonists at peripheral receptors, especially in cases where the pain is associated with inflammation, there has been considerable interest in the development of peripherally selective KOR agonists to avoid the centrally mediated adverse effects [67,70]. Asimadoline has been reported to be a peripherally selective KOR agonist [67] whose transport across the blood–brain barrier (BBB) is limited by the efflux protein P-glycoprotein (P-gp) [71]. The KOR agonist ADL 10–0101 (Adolor Corp., PA, USA) has been reported to be peripherally selective and to decrease pain scores in a preliminary study of patients with chronic pancreatitis [72]. Recently, novel tetrapeptides with KOR agonist activity have been identified that are peripherally selective [73–75], and have entered clinical trials.

Vanderah *et al.* compared two novel, all D-amino acid, tetrapeptide κ-opioid receptor agonists, FE 200665 and FE 200666, to brain-penetrating (enadoline) and peripherally selective (asimadoline) κ-agonists [75]. Both compounds demonstrated agonist activity in the human κ-opioid receptor 1 GTPγ S-binding assay

(EC_{50} of 0.008 nM and 0.03 nM), and resulted in dose-related antinociception in the mouse writhing test (A_{50}: 0.007 and 0.013 mg/kg, intravenously, respectively) [75]. The potency ratios between central and peripheral activity suggest a therapeutic window significantly higher than for previous κ-agonists [75].

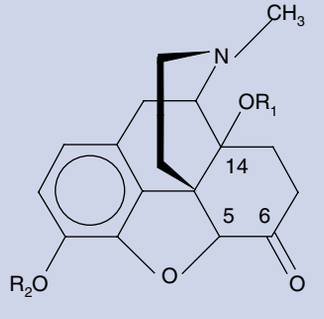
By focusing on 4,5-epoxymorphinan, a traditional opioid skeleton but a new structure in the opioid κ-agonist research field, and by rationally applying the 'message-address concept' and 'accessory site hypothesis', Kawai and colleagues discovered a new chemical class of opioid κ-agonist, TRK-820 [76], which may possess clinical utility as an antipruritus agent.

Endormorphins

Endomorphins are the first reported brain peptides that bind to the μ-receptor with high affinity and selectivity, and so have been referred to as endogenous μ-opioid receptor ligands. Morphine and endomorphins act as agonists at the same μ-opioid receptor, but the latter are thought to inhibit pain without some of the undesired side-effects of plant opiates. Thus, multiple studies have been initiated on the possible use of endomorphin analogs as analgesics instead of morphine [77].

N-methylmorphinan-6-ones

Oxycodone and oxymorphone belong to the chemical class of *N*-methylmorphinan-6-ones. A derivative of oxymorphone, 14-*O*-methyloxymorphone (Figure 1), was developed by our group and described to be approximately 400- and 40-fold more potent than morphine and oxymorphone, respectively, in animal models [78].



Oxycodone: R_1 = H, R_2 + CH_3
14-*O*-methyloxycodone: R_1 = R_3 + CH_3
Oxymorphone: R_1 = R_2 = H
14-*O*-methyloxymorphone: R_1 = CH_3, R_2 + H

Figure 1. *N*-methylmorphinans. Reproduced with permission from [88].

The 4,5-oxygen bridge-opened 6-ketomorphinans have increased affinities to the μ-opioid receptor [78,79], and higher antinociceptive potency [79] than their 4,5-oxygen-bridged analogues. The C-6 carbonyl group of 6-ketomorphinans can be easily chemically modified, and studies have demonstrated that these types of modifications generally do not affect the opioid character of the ligand [80–83]. For example, hydrazone, oxime and semicarbazone derivatives, and amino acid conjugates of *N*-methyl-6-ketomorphinans display high affinity for the μ-opioid receptor, [80–83] and high antinociceptive potencies together with reduced unwanted adverse effects [84–87].

Spetea and colleagues synthesized acrylonitrile incorporated 4,5-oxygen bridge-opened *N*-methylmorphinans (1–3) [88], using a modified van Leusen reaction to introduce the cyano group and to open the 4,5-oxygen bridge simultaneously in a convenient, high-yield one-pot reaction, leading to the 14-hydroxylated and 14-methoxylated 6-cyanomorphinans 1 and 2, respectively [88,89] (Figure 2). In addition, the synthesis of the 4-*O*-methylated derivative of compound 1 (e.g., compound 3) was produced [88].

An examination of the affinities of the 6-cyano target compounds 1–3 reveals that they display high binding affinity in the low nanomolar range to the *í* receptor and are *í* selective. Their binding affinities at the *í* site are 1–2 orders of magnitude higher than the affinities to δ and κ receptors. Compounds 2 and 3 showed affinities to μ receptors comparable or higher than that of morphine, but considerably greater than that of oxycodone [88].

Among the tested compounds, the 6-cyano-3,4-dimethoxy derivative 3 displayed the highest μ affinity (K_i of 2.44 nM) versus morphine (K_i of 6.55 nM) [88].

The 6-cyano-3,4-dimethoxy derivative 3 displayed the highest antinociceptive potency of the three 6-cyanomorphinans, being in the hot-plate test approximately nine- and six-fold, in the tail-flick test approximately 52- and 106-fold, and in the p-phenylquinone writhing test approximately 14- and 15-fold more potent than oxycodone and morphine, respectively [88].

Opioid receptor variants

The analgesic effects of opioids, as well as OIAEs, may be significantly altered by structurally modifying existing opioids (taking advantage of known structure–activity relationships); by modifying the opioid receptor; and/or by modifying the interaction of the opioid analgesic

with the opioid receptor. Multiple variants of the μ-opioid receptor exist, and may modulate pain perception/opioid-induced analgesia perception, as well as possible OIAE perception.

Potential strategies aimed at selectively stimulating or functionally silencing various opioid receptor isoforms. Shabalina *et al.* hypothesized that the *OPRM1* gene possesses several functional elements and SNPs located within this region that alter OPRM1 receptor function. Shabalina and colleagues utilized comparative genome analysis and obtained evidence for the existence of an expanded human *OPRM1* gene locus with new promoters, alternative exons and regulatory elements [90]. Examination of polymorphisms within the human *OPRM1* gene locus identified strong association between SNP rs563649 and individual variations in pain perception. SNP rs563649 is located within a structurally conserved internal ribosome entry site (IRES) in the 5′-UTR of a novel exon 13 containing OPRM1 isoforms (MOR-1K) and affects both mRNA levels and translation efficiency of these variants [90]. Furthermore, rs563649 exhibits very strong linkage disequilibrium throughout the entire *OPRM1* gene locus and thus affects the functional contribution of the corresponding haplotype that includes other functional *OPRM1* SNPs.

Exon 13 containing OPRM1 isoform codes for a 6-transmembrane receptor variant (MOR-1K) that expresses excitatory cellular effects and may represent the molecular mechanisms that contribute to opioid-induced hyperalgesia, dependence and tolerance [90].

Shabalina and colleagues provide evidence for an essential role for MOR-1K isoforms in nociceptive signaling, and suggest that genetic variations in alternative *OPRM1* isoforms may contribute to individual differences in opiate responses, resulting in the wide variations in the pain threshold found in humans subjects [90].

Opioids binding to MOR-1 generally lead to decreased levels of cyclic adenosine monophosphate (cAMP); however, stimulation of the MOR-1K isoform by opioid binding leads to increased cAMP levels, as well as increased nitric oxide release [90]. Higher receptor expression of MOR-1K is associated with hyperalgesia and poor morphine sulfate response. Stimulation of the MOR-1K isoform produces cellular excitation rather than cellular inhibition.

Shabalina *et al.* suggested that the presence of a minor T allele should lead to higher expression levels of corresponding *MOR-1K* isoforms [90]. The localization of a strong functional SNP within the human analog of mouse exon 13 provides evidence for the biological significance of *MOR-1K* isoforms. Shabalina and colleagues showed that *MOR-1K* isoforms with variable exon 13–exon 2 junctions are expressed in a tissue-specific manner and may contribute to tissue-specific post-transcriptional regulation. The *T* allele of rs563649 is associated with higher translation efficiency and higher pain sensitivity. Thus, it is conceivable that opioids binding to and activating the MOR-1K isoform may facilitate pain or promote opioid-induced hyperalgesia.

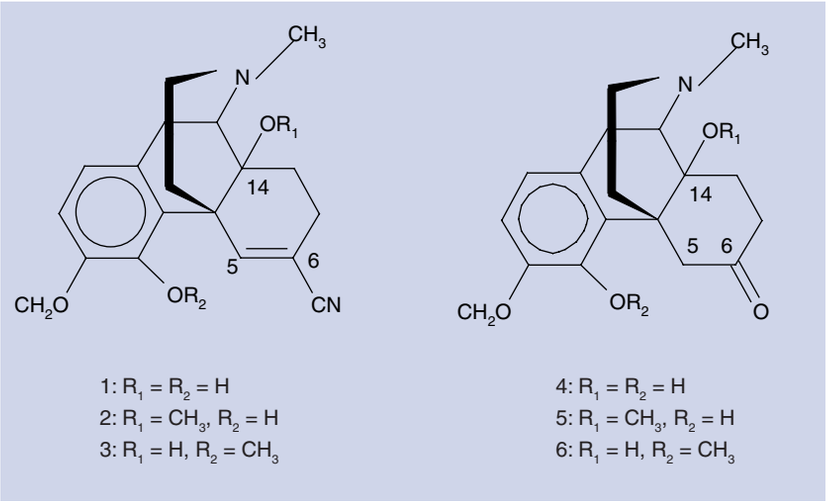


Figure 2. 6-cyanomorphinans. Adapted with permission from [88].

Thus, it appears that opioids may have at least two distinct signaling pathways: one that occurs when opioid agonists bind to the μ-opioid receptor that may produce analgesia, and one which occurs when opioids interact with and stimulate TLR4, which may produce glial activation and contribute to opioid-induced hyperalgesia dependence and tolerance [53]. Opioids may also contribute to the upregulation of TLR4 expression in microglia *in vitro* and *in vivo* [51]. The phenomena of OIH, dependence and tolerance may be ameliorated in TLR4-knockout and TLR4 point mutation mice, by administering TLR4 antisense oligodeoxy nucleotides, TLR4 (an inhibitor of TLR4 downstream signaling) as well as glial inhibitors, or inhibitors of the proinflammatory mediators generated by TLR4 stimulation [53].

Furthermore, it appears that these pathways may be stereospecific. The (-) opioid receptor agonists bind to the MOR, which may contribute to analgesia, but the (+) opioid receptor agonists do not bind to opioid receptors on neurons to produce analgesia. However, the (+) opioid antagonists (e.g., (+) naltrexone, (+) naloxone) may interact with TLR4, and thereby

inhibit its activation by (-) opioid agonists [53]. Fortunately, only (-) opioid receptor antagonists will reverse (-) opioid receptor agonist-induced analgesia. Thus, it is conceivable that a combination product of (-) morphine and (+) naltrexone may produce analgesia without concerns of OIH, dependence and/or tolerance.

Using haplotypic mapping, genes for various receptors and other structures have been associated with specific opioid adaptations. Two of these, the β2 adrenergic receptor and 5-HT3 serotonin receptor were associated with OIH and opioid dependence, respectively. In both cases SNPs within the associated genes probably work by altering expression levels to alter adaptations to opioid administration.

Haplotypic mapping revealed an association of expression of the *Htr3a* gene (which codes for the 5HT3 receptor) with opioid dependence, and there is alteration (e.g., downregulation) of Htr3a expression after chronic morphine exposure, especially in C57 strain animals that display a great deal of opioid dependence [91]. 5HT3 antagonists (e.g., ondansetron) inhibit opioid dependence and also appear to ameliorate opioid withdrawal symptoms in humans [91] and may inhibit OIH and opioid-induced tolerance [48] in animals [91,92]. Haplotypic mapping also revealed an association of expression of the *Adrb2* gene (which codes for the receptor) and opioid-induced hyperalgesia. β-2 adrenergic receptor antagonists inhibited opioid-induced hyperalgesia [93]. β-2 adrenergic receptor antagonists (e.g., butoxamine) also inhibited opioid tolerance and opioid dependence [94]. Thus, it appears that in the future potential combinations of opioids with 5HT3 antagonists and/or β-2 receptor antagonists may yield interesting analgesic cocktails.

Multiple genes have been identified that may function as modulators of opioid pharmacokinetics and/or pharmacodynamics and thus, may potentially affect opioid-induced analgesia or OIAEs. Thus far, notable genes include: *OPRM1* (μ-opioid receptor gene), *COMP* (catechol-*O*-methyltransferase gene involved in catecholamine metabolism), *MC1r* (melancortin 1 receptor gene), *ABCB1* (the gene coding for P-glycoprotein involved in the efflux of opioids from the CNS) and the genes coding for CYP2D6, which is the cytochrome P450 isoenzyme that metabolizes various opioids (e.g., codeine into active hydroxyl analgesics such as morphine).

The most important SNP of the *OPRM1* gene is the substitution of nuecleotide adenine (A) with guanine (G) at position 118 of exon 1 of the gene (118a>G). This substitution, which varies with ethnicity, may result in a decrease in opioid analgesic potency. Tan *et al.* examined the influence of two *OPRM* polymorphisms on acure post-operative pain and morphine usage in women undergoing elective cesarean delivery [95]. Their results suggest that ethnicity and *OPRM* 118A>G genotype are independent and significant contributors to variation in pain perception and post-operative morphine use in patients undergoing cesarean delivery [95].

In contrast to morphine, morphine's active metabolite, morphine-6-glucuronide (M6G), is not metabolized but excreted via the kidneys and exhibits enterohepatic cycling, since it is a substrate for multidrug resistance transporter proteins in the liver and intestines [96]. M6G exhibits a delay in its analgesic effects (blood-effect site equilibration half-life of 4–8 h), which is partly related to slow passage through the blood–brain barrier and distribution within the brain compartment [96]. In humans, the potency of M6G is just half that of morphine. In clinical studies, M6G is well tolerated and produces adequate and long-lasting post-operative analgesia [96]. At analgesic doses, M6G causes similar reduction of the ventilatory response to CO_2 as an equianalgesic dose of morphine, but significantly less depression of the hypoxic ventilatory response. Preliminary data suggests that M6G is associated with less nausea and vomiting than morphine, causing 50 and 75% less nausea in post-operative and experimental settings, respectively [96].

In addition to novel opioid analgesic agents that may interact and produce analgesic largely via actions at the δ-opioid or κ-opioid receptor, or perhaps interact differently with various opioid receptors, another type of opioid analgesic agent are the so-called 'atypical opioids'. Although there may exist many ideas on what characterizes an 'atypical opioid', it has been proposed that any opioid, atypical or otherwise, to be considered a 'clinical significant exogenous opioid', should satisfy two criteria: at least 50% of the agent's significant analgesic action should be attributable to its binding and interaction with an opioid receptor, and the opioid receptor binding inhibition constant (K_i; in μM) should be less than 1 as it is for traditional opioids such as codeine (0.2), D-propoxyphene (0.034) and morphine (0.0022–0.00034) [97].

An example of an atypical opioid is the MORANAM tapentadol. Tapentadol has an opioid receptor-binding inhibition of K_i of 0.096 , and over 50% of its analgesia is due to its interaction with the μ-opioid receptor [98].

Tapentadol is a relatively weak μ-opioid receptor agonist and also inhibits the reuptake of norepinephrine. It possesses potent analgesic activity similar to that of oxycodone, but with less gastrointestinal adverse effects (e.g., nausea, vomiting and constipation [99–101]).

Other 'atypical opioids' may similarly possess dual mechanisms of action. Novel bifunctional peptides exist that are δ-/μ-opioid receptor agonists and neurokinin 1 receptor antagonists. Compounds were synthesized using a two-step combinatorial method for C-terminal modification [102]. In this method, the protected C-terminal-free carboxyl peptide, Boc-Tyr(tBu)-D-Ala-Gly Phe-Pro-Leu-Trp(Boc)-OH, was synthesized as a shared intermediate using Fmoc solid-phase chemistry on a 2-chlorotrityl resin. This intermediate was esterified or amidated in solution phase [102]. The structure–activity relationships showed that the C-terminus acted as not only a critical pharmacophore for the substance P antagonist activities, but also as an address region for the opioid agonist pharmacophore that is structurally distant from the C-terminal [102]. These bifunctional peptides, which are opioid agonists and NK-1 antagonists, may show promise as future 'atypical opioid' analgesic agents [103].

Peripheral acting opioids

It has only been in the past decade that a gradual appreciation of the body's peripheral endogenous opioid analgesic system (PEOAS) has begun. The crucial elements of this system are leukocyte-derived opioids that are secreted from leukocytes accumulating at sites of peripheral inflammation (Figure 3). Inflammation increases peripheral leukocyte-derived opioids, as well as peripheral opioid receptors. Inflammation in the periphery leads to an increase in the number/efficiency of opioid receptors on primary afferent neurons. Attempts to mimic or augment this peripheral analgesic

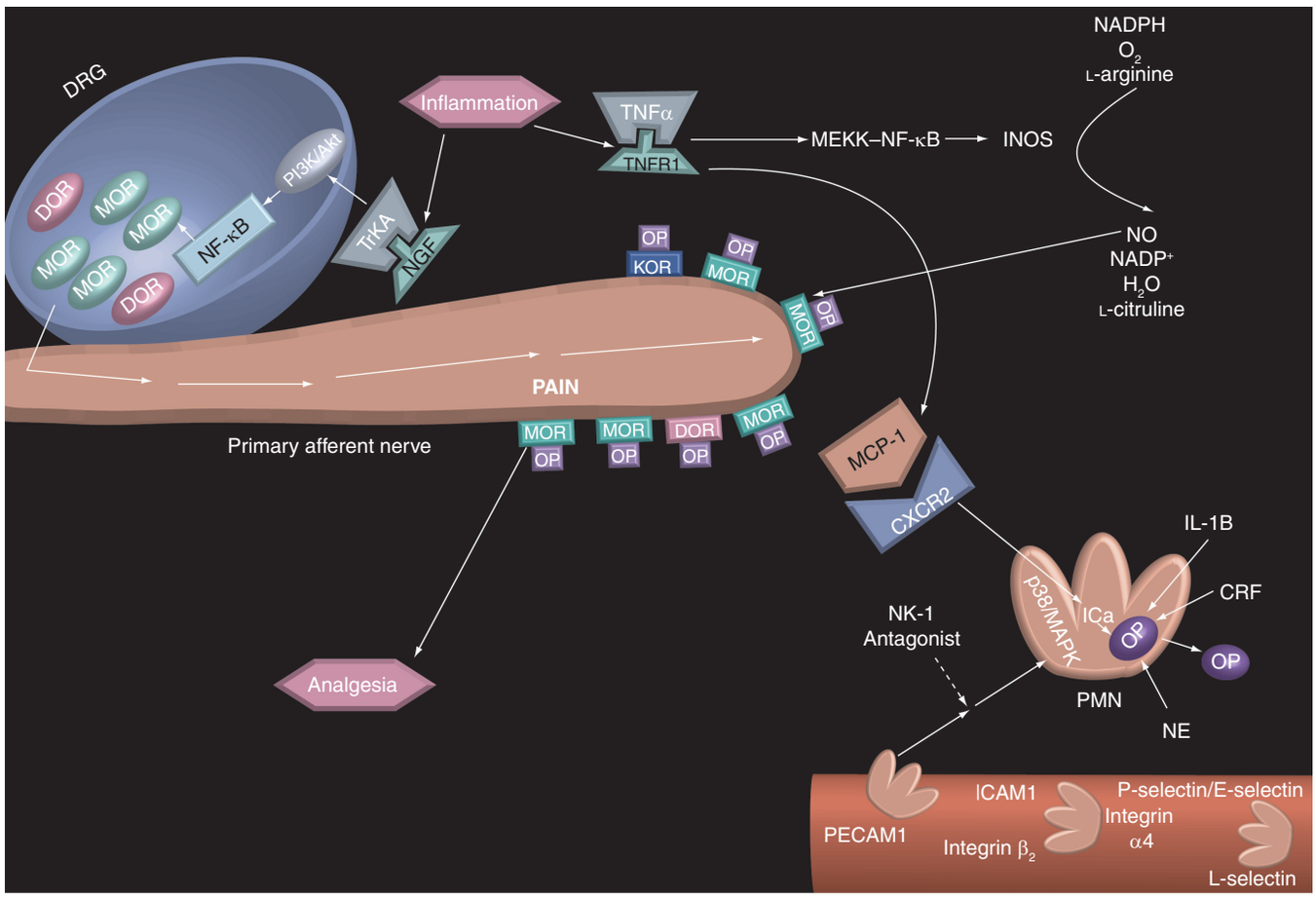


Figure 3. Peripheral endogenous opioid analgesia system.
CRF: Corticotrophin-releasing factor; DOR: δ-opioid receptor; DRG: Dorsal root ganglion; INOS: Inducible nitric oxide synthase; KOR: κ-opioid receptor; MOR: μ-opioid receptor; NE: Norepinephrine; NF: Nuclear factor; NGF: Nerve growth factor; NO: Nitric oxide; OP: Opioid peptide; PMN: Polymorphonuclear cell.
Adapted with permission from [15].

system may potentially yield analgesia without central untoward adverse effects (e.g., respiratory depression, somnolence and addiction). The concept of peripheral opioid analgesia became more accepted when in 1990, following injection into the rodent hindpaw, D-Ala2, *N*-Me-Phe4, Gly5-ol-enkephalin (DAMGO) (a μ-opioid receptor agonist) was believed to exert its antinociceptive effects locally, since the doses administered are too low to have an effect in the CNS. This notion has been supported by the observation that the quaternary compound morphine methyliodide which does not as readily cross the blood–brain barrier and enter the CNS, produced antinociception following intradermal administration into the hindpaw, but not when the same dose was administered systemically (subcutaneously at a distant site).

Furthermore, Guan *et al.* strengthened the case for peripheral opioid analgesia when they examined whether activation of the peripheral MORs could effectively alleviate neuropathic pain in rats after L5 spinal nerve ligation [104]. Systemic loperamide hydrochloride (0.3–10 mg/kg, subcutaneous), a peripherally acting MOR-preferring agonist, dose-dependently reversed the mechanical allodynia at day 7 post-spinal nerve ligation [104]. This anti-allodynic effect produced by systemic loperamide (1.5 mg/kg, subcutaneous) was blocked by systemic pretreatment with either naloxone hydrochloride (10 mg/kg, intraperitoneal) or methyl-naltrexone (5 mg/kg, intraperitoneal), a peripherally acting MOR-preferring antagonist. It was also blocked by ipsilateral intraplantar pretreatment with methyl-maltrexone (43.5 μg/50 μl) and the highly selective MOR antagonist CTAP (5.5 μg/50 μl) [104]. The data of Guan and colleagues suggests that loperamide can effectively attenuate neuropathic pain, primarily through activation of peripheral MORs in local tissue [104].

Although peripheral opioid receptors are largely expressed by primary sensory neurons [105], they are functionally inactive under most basal conditions. However, with tissue injury/inflammation, the action of bradykinin on the B2 receptor improves efficiency of MOR coupling to Gα and promotes MOR signaling [106].

Opioid analgesics with restricted access to the CNS PAOs may possess improved safety over opioids currently used in clinical practice, with less OIAEs [107]. Obara *et al.* demonstrated peripheral antinociception of μ-opioid receptor agonists, morphine, DAMGO, endomorphin-1, and endomorphin-2 in neuropathic pain elicited by sciatic nerve ligation [108]. All these agonists were more effective in alleviating allodynia after their intraplantar, than after subcutaneous administration. Their antinociceptive effects appear to be mediated by local peripheral opioid receptors, since the peripherally selective opioid receptor antagonist, naloxone methiodide, blocked the analgesia. Thus, this is in line with most of the studies reporting morphine effects after peripheral administration [109–111].

Recently, 6-amino acid-substituted derivatives of 14-*O*-methyloxymorphone were described as μ-opioid receptor agonists with restricted penetration to the CNS [83,112]. Published pharmacological data from Furst *et al.* demonstrated that such derivatives produce long-lasting antinociception in acute inflammatory pain after subcutaneous administration, being more potent than morphine [87]. It was also shown that morphine, a centrally acting μ-opioid agonist, exerts its analgesic effects by both central and peripheral mechanisms, while the new opioids interact primarily with peripheral opioid receptors. Obara *et al.* assessed the antinociceptive effects of the 6-amino acid conjugates (glycine and phenylalanine), α- or β-orientated, 14-*O* methyloxymorphone (Figure 4) in rat models of inflammatory pain (induced by local intraplantar formalin injection) and neuropathic pain (produced by ligation of the sciatic nerve) after local intraplantar administration directly into the injured hindpaw, and compared their antinociceptive effects to morphine [107].

Intraplantar administration of morphine and the 6-amino acid derivatives produced dose-dependent reduction of formalin-induced flinching of the inflamed paw, without significant effect on the paw edema [107]. Local intraplantar administration of the new derivatives in rats with neuropathic pain induced by sciatic nerve ligation produced antiallodynic and antihyperalgesic effects; however, the antinociceptive activity was lower than that observed in inflammatory pain [107]. In both models, the 6-amino acid derivatives and morphine at doses that produced analgesia after intraplantar administration were systemically (subcutaneous) much less active, indicating that the antinociceptive action is due to a local effect [107]. Moreover, the local opioid antinociceptive effects were significantly attenuated by naloxone methiodide, a peripherally acting opioid receptor antagonist, demonstrating that the effect was mediated by peripheral opioid receptors [107]. Obara *et al.* suggested their data indicate that the peripherally restricted 6-amino acid conjugates of 14-*O*-methyloxymorphone elicit antinociception after local administration, being more potent in inflammatory than in neuropathic pain [107].

In some cases adverse effects may be reduced by utilizing agents that specifically target transport mechanisms that contribute to opioids gaining access to the CNS, thus essentially making them 'functionally peripherally restricted'. Still other strategies may aim to reduce the opioid concentration in the CNS by modulation of blood–brain barrier function. Preliminary attempts to show that LNS5662 (flavonol–P-gp modulator) – a flavonol thought to activate P-gp efflux of pump ligands at the blood–brain barrier – may ameliorate opioid adverse effects in OINV, thereby improving tolerability without interfering with analgesic efficacy. This agent may therefore deserve further study [113].

Opioids with reduced P-gp substrate activity, a series of known 3- and 6-hydroxy, -methoxy and -desoxymorphine analogs, were synthesized and analyzed for P-gp substrate activity and opioid binding affinity [114]. 6-desoxymorphine showed high affinity for opioid receptors and did not induce P-gp-mediated ATP hydrolysis. 6-desoxymorphine demonstrated morphine-like antinociceptive potency in mice, suggesting that it may be useful in evaluating the role of P-gp in the development of analgesic tolerance to opioid therapy [114].

Conclusion

Although there are a significant number of patients who may achieve adequate opioid-induced analgesia with tolerable adverse effects; many patients may experience OIAEs that occur frequent enough and intense enough to limit the analgesic efficiency of opioid analgesic therapy. The use of various strategies that include: the future use of peripherally-restricted opioid analgesics, alternative opioid analgesics, agents to alter the expression of various opioid receptors or employing a second agent (combination opioid analgesics) may potentially provide optimal analgesia with minimal adverse effects. Combinations of opioids with ultra-low dose opioid antagonists appear to be closest to market availability; however, peripherally acting opioids and opioids with TLR4 antagonists may be the most promising agents at this juncture.

Future perspective

In the future, peripherally acting opioids may be developed to provide potent analgesia with minimal adverse effects. Genetically, functionally altered opioid receptors may be beneficial as well. Alternative exons of *OPRM1* may represent variable regions of *OPRM1*, and may be specifically targeted for future genetic tests and treatment strategies.

Theoretically, therapeutic strategies aimed at novel opioid formulations designed not to bind to or activate the MOR-1A may possess potential clinical utility. Alternatively, therapeutic strategies aimed at 'functionally silencing' the MOR-1K isoform may also possess potential clinical utility. Other potential future strategies may include impeding or disrupting aspects or components of MOR downstream signaling, perhaps via inhibitors of ERK phosphorylation, inhibitors of glial activation and/or TLR4 antagonists.

In addition, there are many more potential therapeutic avenues that may be explored in the future in attempts to improve opioid-induced effects that may be counter-productive to goals of optimal analgesia with minimal adverse effects. Inhibitors of spinal ceramide biosynthesis and/or facilitators of spinal ceramide metabolism may be of interest in this regard, as well as agents that may reduce concentrations of peroxynitrite generation or contribute to 'quenching' of existing peroxynitrite.

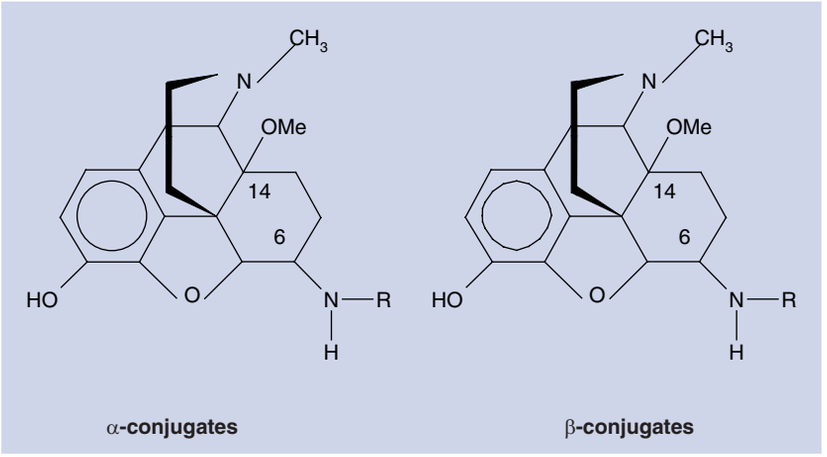


Figure 4. Peripheral-acting opioids. Adapted with permission from [95].

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Executive summary

- Opioid-induced adverse effects (OIAEs) represent a significant obstacle in efforts to achieve optimal analgesia with minimal adverse effects.
- Conventional strategies aimed at ameliorating OIAEs may include:
  - The use of κ-opioid receptor agonists to diminish opioid-induced nausea/vomiting (OINV);
  - The use of morphine-like opioids without the 6-hydroxyl group on the structure of morphine in efforts to diminish OINV;
  - The use of antiemetics, opioid rotation and/or the use of opioid-sparing analgesic agents/strategies.

Three future strategies that may ameliorate many OIAEs include:

- The use of additional agents that either minimize the occurrence/frequency/severity of OIAEs or potentiate opioid analgesia (e.g., provide analgesic synergy) so that the dose of opioid required for the same level of analgesia is reduced (e.g., combination opioid analgesics):
  - 5HT3 antagonists
  - β2-adrenergic antagonists (-) morphine and (+) naltrexone
- The use of 'alternative opioid analgesics' having nontraditional functional interactions with various opioid receptors (e.g., selective δ-opioid receptor agonists) or 'atypical opioids' having opioid properties/characteristics, as well as nonopioid properties/characterisitics (e.g., μ-opioid receptor agonist/noradrenergic modulators [tapentadol]).
- The use of peripheral acting opioids.

Future attempts aimed at ameliorating OIAEs may also include:

- 'Functionally' silencing the MOR-1K isoform.
- Quenching peroxynitrite.
- Inhibitors of spinal ceramide biosynthesis.

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