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Focused Review

Combination Opioid Analgesics

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Although there is no "ideal analgesic," scientists and clinicians alike continue to search for compounds with qualities which may approach the "ideal analgesic." Characteristics of an "ideal" analgesic may include: the agent is a full agonist providing optimal/maximal analgesia for a wide range/variety of pain states (e.g., broad spectrum analgesic activity), it does not exhibit tolerance, it produces no unwanted effects and minimal adverse effects, it has no addictive potential, it does not facilitate pain/hyperalgesia, it has a long duration, it has high oral bioavailability, it is not vulnerable to important drug interactions, it is not significantly bound to plasma proteins, it has no active metabolites, it has linear kinetics, and it is eliminated partly by hydrolysis to an inactive metabolite (without involvement of oxidative and conjugative enzymes). Investigators have concentrated on ways to alter existing analgesics or to combine existing analgesic compounds with compounds which may improve efficacy over time or minimize adverse effects. The addition of an analgesic with a second agent (which may or may not also be an analgesic) to achieve a "combination analgesic" is a concept which has been exploited for many years. Although there may be many reasons to add 2 agents together in efforts to achieve analgesia, for purposes of this article — reasons for combining an opioid with a second agent to produce a combination opioid analgesic may be classified into 6 major categories: 1.) combinations to prolong analgesic duration; 2.) combinations to enhance or optimize analgesic efficacy (e.g., analgesic synergy); 3.) combinations to diminish or minimize adverse effects; 4.) combinations to diminish opioid effects which are not beneficial (or contrariwise to or enhance beneficial opioid effects); 5.) combinations to reduce opioid tolerance/opioid-induced hyperalgesia; and 6.) combinations to combat dependency issues/addiction potential/craving sensations. Combination opioid analgesics are one avenue which may give rise to "pain pills" with improved analgesic profiles over existing analgesic medications.

Key words: Pain, combination opioid analgesic, tolerance, opioid-induced hyperalgesia.

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The addition of an analgesic with a second agent (which may or may not also be an analgesic) to achieve a "combination analgesic" is a concept which has been exploited for many years. Although there may be many reasons to add 2 agents together in efforts to achieve analgesia, for purposes of this article — reasons for combining an opioid with a second agent to produce a combination opioid analgesic (COA) may be classified into 6 major categories:

1. Combinations to prolong analgesic duration
2. Combinations to enhance or optimize analgesic efficacy (e.g., analgesic synergy)
3. Combinations to diminish or minimize adverse effects
4. Combinations to diminish opioid effects which are not beneficial (or contrariwise to or enhance beneficial opioid effects)
5. Combinations to reduce opioid tolerance/opioid-

induced hyperalgesia (OIH)

6. Combinations to combat dependency issues/addiction potential/craving sensations

The "second nonopioid agent" may be referred to by some as a "coanalgesic" or "adjuvant analgesic." The advantages of combining 2 agents should clearly outweigh any drawbacks of the added agents. Some agents added to opioids may work in multiple categories. Combining 2 agents with distinctively different properties solely for the convenience of taking 1 pill is not considered a COA.

1. Combinations to Prolong Analgesic Duration

Attempts at increasing opioid duration/effects by modifying endogenous opioid metabolism have thus far not met with great success. The 2 enzymes which are primarily responsible for the degradation of enkephalins in vivo are neutral endopeptidase ([NEP], enkephalinase) and amino peptidase N (APN), with APN playing a predominant role in the brain. NEP also can degrade or inactivate multiple peptides including proinflammatory peptides, substance *P*, bradykinin, and opioid peptides (e.g., Met-enkephalins and Leu-enkephalins, β–endorphins, and dynorphins). RB 3007, a dual inhibitor of these 2 enzymes, exhibited antinociception in animal pain models as well as antinociceptive synergism when coadministered in conjunction with subanalgesic doses of methadone or cholecystokinin B (CCKB) receptor antagonists (e.g., PD-134, 308) (1). Additionally, pro-drugs of phosphinic dual inhibitors of NEP and APN may result in long lasting antinociception (2).

2. Combinations to Enhance Analgesic Efficacy

Opioids and Norepinephrine Transporter Modulators

Various COAs may be well suited for nociceptive inflammatory pain (e.g., lumiracoxib/codeine) with others being better suited for neuropathic pain (e.g., gabapentin/morphine).

It is conceivable that the interaction of muopioid receptor (MOR) agonists with inhibitors of norepinephrine reuptake may lead to improved analgesia, and 1 agent, tapentadol (which is not FDA approved in the U.S. yet), possesses both of these characteristics. Although tapentadol exhibits weak interactions at both MORs and norepinephrine transporters (NETs), 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 interaction between norepinephrine and opioids is found to yield improved analgesia, then perhaps a norepinephrine reuptake inhibitor [NRI] (e.g., Reboxetine) with an opioid may be a reasonable COA to pilot.

Tai et al (3) performed a study to evaluate the effects of the tricyclic antidepressant amitriptyline on morphine tolerance in rats. Morphine induced antinociceptive tolerance and down-regulation 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 up-regulated GLAST and GLT-1 expression (3). On day 5, morphine challenge (10 microg/10 microl) resulted in a significant increase in levels of excitatory amino acids (EAAs), aspartate, and glutamate in CFS dialysates in morphine-tolerant rats. Amitriptyline coinfusion not only markedly suppressed this morphine-evoked EAA release, but also preserved the antinociceptive effect of acute morphine challenge at the end of infusion (3). Glial cells' activation and increased cytokine expression (TNFalpha, IL-1beta, 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 coinfusion (3). Their results show that amitriptyline not only attenuates morphine tolerance, but also preserves its antinociceptive effect. The mechanisms involved may include (a) inhibition of proinflammatory cytokine expression, (b) prevention of glutamate transporter down-regulation, and even up-regulation of spinal glial (GT) GLAST and GLT-1 expression, with (c) attenuation of morphine-evoked EAA release following continuous long-term morphine infusion (3).

Opioids and Anti-inflammatory Agents

Ortiz and Castaneda-Hernández (4) examined the possible pharmacological interaction between lumiracoxib and codeine or nalbuphine at the local peripheral level in the rat using the 1% formalin test and isobolographic analysis (4). Lumiracoxib, codeine, nalbuphine, or fixed-dose ratios lumiracoxib–codeine or lumiracoxib–nalbuphine combinations were administrated locally in the formalin-injured paw and the antinociceptive effect was evaluated using the 1% formalin test (4). All treatments produced a dose-dependent antinociceptive effect. ED_{40} values were es-

timated for the individual drugs and an isobologram was constructed (4). The derived theoretical ED_{40}'s for the lumiracoxib–codeine and lumiracoxib–nalbuphine combinations were 423.4 ± 31.3 µg/paw and 310.9 ± 24.2 µg/paw, respectively, being significantly higher than the actually observed experimental ED_{40} values, 233.2 ± 30.9 µg/paw and 132.7 ± 11.6 µg/paw, respectively (4). These results correspond to a synergistic interaction between lumiracoxib and opioids at the local peripheral level, potency being about 2 times higher with regard to that expected from the addition of the effects of the individual drug (4). Data suggest that low doses of the lumiracoxib–opioids combination can interact synergistically at the peripheral level and therefore this drug association may represent a therapeutic advantage for the clinical treatment of inflammatory pain (4).

Opioids and Calcium Channel Alpha-2 Delta Ligands

Eckhardt et al (5) investigated, in a randomized, placebo-controlled double-blinded study, the pharmacodynamic and pharmacokinetic interaction of gabapentin and morphine in 12 healthy male volunteers. A significant increase in pain tolerance was observed comparing the combination of morphine and gabapentin (75.5% x h, 95% CI: 54.0-96.9) with morphine + placebo (40.6% x h, CI: 19.2-62.0).

Concerning the pharmacokinetic variables of morphine and its glucuronides, no significant difference between morphine + placebo and morphine + gabapentin was observed, whereas the area under the curve of gabapentin (43.9 ± 5.3 vs 63.4 ± 16.2 microg. H(-1). mL(-1), $P < 0.05$) significantly increased, and apparent oral clearance (230.8 ± 29.4 mL/min vs 178 ± 20.6 vs 73.0 ± 24.2 mL/min, $P = 0.067$) of gabapentin decreased when morphine was administered concomitantly. These results suggest 2 different sites for the pharmacokinetic interaction — one at the level of absorption and the other at the level of elimination, leading to increases in the plasma concentration of gabapentin when morphine was administered concomitantly. Eckhardt and colleagues reveal both a pharmacodynamic and pharmacokinetic interaction between morphine and gabapentin, leading to an increased analgesic effect of morphine + gabapentin (5).

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 (6), in a randomized, double-blind, active placebo–controlled, 4-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.

Of 57 patients who underwent randomization (35 with diabetic neuropathy and 22 with postherpetic neuralgia), 41 completed the trial. Mean daily pain (on a scale from 0 to 10, with higher numbers indicating more severe pain) at a maximal tolerated dose of the study drug was as follows: 5.72 at baseline, 4.49 with placebo, 4.15 with gabapentin, 3.70 with morphine, and 3.06 with the gabapentin–morphine combination ($P<0.05$ for the combination versus placebo, gabapentin, and morphine). 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 ($p < 0.05$ for the combination versus placebo, gabapentin, and morphine). The maximal tolerated doses of morphine and gabapentin were lower ($p < 0.05$) with the combination than for each drug as a single agent (6).

Gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent, with constipation, sedation, and dry mouth as the most frequent adverse effects.

Keskinbora et al (7) compared the effectiveness and safety of gabapentin combined with an opioid versus opioid monotherapy for the management of neuropathic cancer pain in 63 cancer patients who were receiving opioid therapy and reported sufficient pain relief of nociceptive, but not neuropathic, pain. Patients were randomized to 1 of the following treatment protocols:

1) gabapentin adjuvant to ongoing opioid treatment titrated according to pain response while opioid dose was kept constant (group GO) or
2) continuation of opioid monotherapy according to the World Health Organization treatment ladder approach (group OO) (7). Changes in pain intensity, allodynia, side effects, and analgesic drug consumption were evaluated at Day 4 and Day

13 (7). Both treatments resulted in a significant reduction of pain intensity at Day 4 and Day 13 compared to baseline. However, mean pain intensity for burning and shooting pain was significantly higher in the OO group compared to the GO group at both the fourth ($P = 0.0001$) and thirteenth ($P = 0.0001$) days of the study (7). An earlier significant decrease (at Day 4, $P = 0.002$) was observed for allodynia in the GO group compared to the OO group. The rate of side effects in the GO group was significantly lower than that in the OO group ($P = 0.015$). These data suggest that gabapentin added to an opioid provides better relief of neuropathic pain in cancer patients than opioid monotherapy; this combination of gabapentin and an opioid may represent a potential first-line regimen for the management of pain in these patients (7).

Opioids and Local Anesthetics

Neuraxial analgesia is often provided using a mixture of local anesthetics and opioids, which yield analgesic synergy (8). This synergistic combination of agents provides better pain relief and is generally associated with fewer side effects than when either drug is given alone. Local anesthetics have been shown to alter signaling of other G protein-coupled receptors, but little is known about their effect on opioid receptor signaling. Because opioids produce analgesia at least in part by inhibiting presynaptic calcium channels, Komai and McDowell (9) evaluated the effects of tetracaine and bupivacaine on opioid-mediated inhibition of calcium channels in dorsal root ganglion neurons (DRG). The μopioid specific agonist DAMGO (1 μM) inhibited calcium channels in both the absence and presence of tetracaine (50 or 100 μM). However, the extent of DAMGO inhibition in the presence of both concentrations of tetracaine was less than that observed in the absence of tetracaine. DAMGO inhibition decreased from 39.2 ± 24.4% in control to 34.2 ± 24.4% with 50 μM tetracaine ($n = 16$; $P < 0.05$), and from 40.5 ± 19.6% in control to 34.6 ± 20.5% with 100 μM tetracaine ($n = 10$; $P < 0.05$). Similar results were seen with bupivacaine. Tetracaine also decreased the voltage-dependent facilitation of calcium channel currents when G proteins were activated by either DAMGO or the nonhydrolyzable GTP analogue (GTPγS), suggesting that tetracaine weakens the interaction between G protein βγ subunits and the calcium channel. Overall, these results suggest that local anesthetics decrease opioid inhibition of calcium channel activity by interfering with the GTP-mediated signal transduction between opioid receptors and calcium channels (9). Theoretically, the combination of bupivacaine and opioids may affect opioid tolerance by inhibiting the activation of pERK (10), and thus, potentially interfering with NMDAR functions (11), whereas lidocaine does not appear to affect opioid tolerance (12).

The combination of continuous (IT) morphine and bupivacaine for the treatment of cancer pain resulted in a diminished progression of the (IT) morphine dose (slope of regression line = 0.0003 vs 0.005. $P = 0.0001$) during a phase of stable analgesia in comparison with the morphine group (13). Van Dongen and colleagues (13) concluded that the diminished (IT) morphine dose increase in the combination group is considered to be due to a synergistic effect of bupivacaine on the (IT) morphine-induced antinociception. A dose increment during long-term (IT) infusion in cancer patients appears to be related to both disease progression and tolerance (13).

Mercadante et al (14) evaluated the clinical response to a combination of (IT) morphine and levobupivacaine in advanced cancer patients who were highly opioid-tolerant, being previously treated with multiple opioid trials unsuccessfully. Statistical differences in pain intensity were found at the different time intervals. Significant decreases in the intensity of drowsiness and confusion were found after starting (IT) therapy (14). Systemic opioids equivalents significantly decreased. Mercadante and colleagues found that (IT) opioids in combination with local anesthetics (at the most convenient clinical doses) provided long-term improvement of analgesia, with a decrease in adverse effects and opioid consumption until death, in cancer patients who were unresponsive to multiple adequate trials of systemic opioids with persistent poor pain control and/or significant adverse effects (14).

Opioids and Alpha-2 Adrenergic Agonists

Fairbanks and Wilcox (15) demonstrated that spinal antinociceptive synergism between morphine and clonidine persists in mice made acutely or chronically tolerant to morphine.

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 (15). In all tolerant and control groups, the combination of morphine and clonidine produced a significantly less ED50 value than the corresponding theoretical additive ED50 value (15). 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 (15).

Opioids and Calcium Channel Blockers

Gupta and colleagues (16) injected different doses of morphine and nimodipine (5 µg of morphine, 5 µg of nimodipine, 5 µg each of morphine and nimodipine, 10 µg of morphine, 10 µg of nimodipine, 10 µg morphine with 5 µg nimodipine, and 5 µg of morphine with 10 µg of nimodipine) intrathecally in Wistar rats to characterize their antinociceptive effect.

Coadministration of both morphine and nimodipine led to significantly higher antinociception than morphine alone, and the combined antinociceptive action of morphine 5 microg and nimodipine 10 microg was not significantly different from 10 µg of morphine alone, which indicated synergistic interaction (16).

Naloxone (5 mg/kg) could reverse this antinociceptive effect of morphine–nimodipine combination, though it failed to reverse nimodipine (5 µg)-mediated antinociception at 15 min (16). No obvious side effects were noted after administration of either morphine or nimodipine, or both.

Opioids and Cannabinoids

Cox et al (17) revealed that isobolographic analyses indicated a synergistic interaction between Delta(9)-THC and morphine in both nonarthritic and arthritic rats.

Smith et al (18) demonstrated that low dose THC-morphine combination treatment produces antinociception in the absence of tolerance or attenuation of receptor activity.

Narang et al (19) assessed the efficacy of dronabinol (Marinol capsules; Solvay Pharmaceuticals, Brussels, Belgium), a synthetic Δ^9-THC (tetrahydrocannabinol), in 30 patients taking opioids for chronic pain to determine its potential analgesic effects as an adjuvant treatment. Phase I of this 2-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 3, 8-hour visits (19). Results of the Phase I study showed that patients who received dronabinol experienced decreased pain intensity and increased satisfaction compared with placebo (19). 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 side effects was dose related. Overall, the use of dronabinol was found to result in additional analgesia among patients taking opioids for chronic noncancer pain. Their study examines the effect of adding a cannabinoid to the regimen of patients with chronic pain who report significant pain despite taking stable doses of opioids. The results of this preliminary study suggest that dronabinol, a synthetic THC, may have an additive effect on pain relief (19). Furthermore, Powell et al (20) suggested that activation of spinal calcitonin gene related peptide (CGRP) receptors contributes to both the development and expression of spinal opioid tolerance. Trang et al (21) suggested that activation of CGRP and substance *P* receptors, at the spinal level, contributes to the induction and expression of opioid physical dependence. Coadministration of acute or chronic morphine with a CB1-receptor antagonist/inverse agonist, 1-(2, 4-dichlorophenyl)-5-(4-idodophenyl)-4-methyl-N-1-piperidinyl-1H-pyrazole-3-carboxamide (AM-251), inhibited the development of both acute and chronic analgesic tolerance (22). In animals already exhibiting tolerance to morphine, intervention with AM0251 restored morphine analgesic potency. Coadministration with AM0251 attenuated the morphine-induced increase in CGRP-immunoreactivity in the spinal cord and in DRG cultured neurons (22). Collectively, the results of the study by Trang et al (22) suggest that activity of endocannabinoids, mediated via CB1-receptors, contributes to both the development and maintenance of opioid tolerance by influencing the opioid-induced increase in spinal CGRP.

Opioids and GABA B Agonists

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 (23).

Baclofen (Lioresal®) may also show similar effects in humans, effects that are also dependent upon pattern as well as level of cocaine exposure (24). In a randomized placebo-controlled investigation conducted by Shoptaw and colleagues (24) , evidence of initial baclofen (Lioresal®) efficacy was found over placebo in reducing cocaine use when concurrently administered with thrice weekly substance abuse counseling sessions. Within this particular investigation, the clinical effects of baclofen were more pronounced in those with chronic levels of cocaine use at baseline (24). Although study limitations included small sample size as well as the rate of attrition, the results may warrant support for full-scale efficacy trials of baclofen (Lioresal®) among patients with chronic cocaine dependence (24).

Additionally, baclofen has been shown to possess antinociceptive properties in preclinical studies [perhaps largely by affecting thalamic processing] (25,26) as well as in clinical trials (27-29). Hara and colleagues (30) examined the effects of intrathecally coadministered morphine and muscimol or baclofen on somatic and visceral antinociception in rats. The tail flick (TF) test and colorectal distension (CD) test were used to assess somatic and visceral antinociceptive effects, respectively. The measurements were performed for 180 min after the (IT) administration of morphine (0.1-10 micrograms), muscimol (0.2-10 micrograms), baclofen (0.03-1 microgram), combination of morphine and muscimol or baclofen, or saline. Morphine, muscimol, or baclofen increased both TF latency and CD threshold in a dose-dependent fashion. Although morphine 0.1 microgram, muscimol 0.2 microgram, or baclofen 0.03 microgram alone did not significantly increase TF latency and CD threshold, the combination of morphine 0.1 microgram and muscimol 0.2 microgram or baclofen 0.03 microgram significantly increased both TF latency and CD threshold. The coadministration of muscimol or baclofen increased the antinociceptive effects of morphine in intensity and duration (30).

L-baclofen may possess even greater antinociceptive properties, potentially yielding improved analgesia for trigeminal neuralgia versus racemic baclofen (31). Anecdotal reports regarding (IT) administration of baclofen for pain relief exist (32,33). It has also been suggested that baclofen may be potentially used in the management of alcohol withdrawal syndrome (34) and opioid withdrawal syndrome (35). 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 (36). Therefore, baclofen may have a place in the therapeutic armamentarium for pain and chemical dependency — and potential future combination products (e.g., morphine and baclofen ["morphlofen"]) may be of interest (11).

Opioids and Glial Inhibitors

Antiallodynic and antihyperalgesic effects of morphine (10 mg/kg; intraperitonal (IP) injection) were significantly potentiated in groups preemptively and repeatedly injected with minocycline (von Frey test, 18 g versus 22 g; cold plate test, 13 s versus 20 s in rats and 1.2 g versus 2.2 g; 7.5 s versus 10 s in mice; respectively) or pentoxifylline (1.3 g versus 3 g; 7.6 s versus 15 s in mice; respectively) (37). Antiallodynic and antihyperalgesic effects of IT morphine (30 µg; IT in mice were also significantly potentiated in the minocycline-treated group (1.2 g versus 2.2 g; 7.5 s versus 11 s; respectively) (37). Mika et al (37) suggested that these findings indicate that preemptive and repeated administration of glial inhibitors may suppress the development of allodynia and hyperalgesia, and potentiate the antinociceptive effects of morphine in rat and mouse models of neuropathic pain.

Opioids and Other Agents

In the future, "designer" combinations tailored to specific populations where opioids administered alone could yield suboptimal analgesia may be available. For example, a combination of IL-4 (or IL-4 receptor agonist or enhancer) and opioid may yield improved analgesia versus opioids alone in those patients with diminished functional activity of IL-4 and/or reduced opioid receptor expression (11). ([IL-4 induces and upregulates the transcription of (MOR) and delta opioid receptors (*DOR*s) via a STAT6-binding site [(38-40)].

Singal et al (41) concluded that increased NO formation may be responsible for the decreased antinociceptive effects of morphine in diabetic mice and that green tea extract (GTE) restored the antinociceptive effects of morphine by inhibition of NO production.

To clarify the role of the NMDA receptor on the morphine-induced antinociception at the supraspinal level, Yoshikawa and colleagues (42) investigated the effects of the intracerebroventricular (ICV) adminis-

tration of D-serine, a selective agonist for the glycine site of the NMDA receptors, alone or in combination with morphine using the (TF) test. The potentiation of the antinociception produced by both D-serine alone or in combination with morphine was dose-dependently attenuated by the ICV administration of L-701,324, a selective antagonist for the glycine site of the NMDA receptors (42). In addition, the potentiation of the D-serine-induced antinociception was antagonized by the ICV administration of naloxone, a non-selective opioid receptor antagonist (42). Yoshikawa et al suggested that the activation of the supraspinal NMDA receptors by D-serine leads to the potentiation of the antinociception in the TF test and that endogenous D-serine could modulate the μopioid receptor mediated antinociception via the glycine site of the NMDA receptors at the supraspinal level.

Ugolini et al (43) demonstrated that MNAC13, the only anti-TrkA monoclonal antibody for which functional neutralizing properties have been clearly shown both in vitro and in vivo, induces analgesia in both inflammatory and neuropathic pain models, with a surprisingly long-lasting effect in the latter. The formalin-evoked pain licking responses are significantly reduced by the MNAC13 antibody in CD1 mice (43). Treatment with the anti-TrkA antibody also produces a significant antiallodynic effect on neuropathic pain. Repeated IP injections of MNAC13 induce significant functional recovery in mice subjected to sciatic nerve ligation, with effects persisting after administration (43). A clear synergistic effect is observed when MNAC13 is administered in combination with low doses of opioids that are not efficacious alone, per se (43).

3. Combinations to Reduce Adverse Effects

An agent which is added to an opioid in efforts to reduce adverse effects is generally designed to combat specific adverse effect. The use of very low doses to MOR antagonists added to opioids may help ameliorate adverse effects which occur from activation of MORs.

Other strategies to reduce side effects may be directed toward attempts to inhibit or diminish the functionality of active opioid metabolites, since some side effects may occur in part from active metabolites. Still other strategies may aim to reduce the opioid concentration in the central nervous system (CNS) by modulation of blood-brain barrier function.

Preliminary attempts to show that LNS5662 (Flavonol-PgP Modulator) — a flavonol thought to activate PgP efflux of pump ligands at the bloodbrain barrier — may ameliorate opioid adverse effects in opiod-induced nausea/vomiting (OINV), thereby improving tolerability without interfering with analgesic efficacy. This agent may therefore deserve further study (44).

Strategies aimed at reducing specific opioid-induced adverse effect(s) generally utilize agents which are known to treat the specific effect(s). For example, although OINV has not been extensively studied by itself (most of the work is associated with postoperative nausea and vomiting [(PONV)], many antiemetic agents could potentially be trialed in combination with opioids, in efforts to minimize OINV.

In clinical settings, multiple receptors may play a role in contributing to nausea/vomiting. Some of the "emetogenic" receptors that have been proposed are dopamine-2 (D2), histamine-1 (H1), *DOR*, 5-hydroxytryptamine (serotonin) (5-HT3), acetylcholine (ACh), neurokinin-1 (NK-1), and cannabinoid receptor-1 (CB1). Antimemetics that work at or antagonize these receptors include the following:

- D2—haloperidol
- H1—promethazine
- DOR—naloxone
- 5-HT3—Ondansetron
- ACh—Scopolamine
- NK-1—Aprepitant
- CB1—Dronabinol

Although aprepitant has not been studied for alleviating "pure" OINV, it seems, intuitively, that it could be a promising agent for this purpose. The acute administration of morphine may cause an increase in CNS expression of substance *P* (45). Furthermore, morphine up-regulates 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 (46). Therefore, it does not seem unreasonable to study aprepitant — an NK-1R antagonist used for the treatment of PONV and chemotherapy-induced nausea/vomiting, CINV — for its efficacy in treating OINV. "Aprepioid," a hypothetical COA of aprepitant and an opioid, may be an interesting combination to pilot.

4. Combinations to Diminish Opioid Effects Which Are Not Beneficial

Chronic morphine treatment stimulates angiogenesis and tumor growth in mice (47). Farooqui et al (47) reported that 2 weeks of chronic morphine treatment at clinically relevant doses stimulates COX-2 and PGE(2) (4.5-fold compared to vehicle alone) and angiogenesis in breast tumors in mice. This is accompanied by increased tumor weight (approximately 35%), increased metastasis, and reduced survival. Coadministration of celecoxib prevents these morphine-induced effects. In animal models, celecoxib prevents morphine-induced stimulation of COX-2, PGE(2), angiogenesis, tumor growth, metastasis, and mortality, as well as providing significantly better analgesia than with morphine or celecoxib alone (47).

5. Combinations to Reduce Opioid tolerance/opioid-induced Hyperalgesia

Many changes may occur following chronic exposure to opioids which may include modulation of the activity of the various isomers of adenylyl cyclase activity, modulation of the balance between various kinases and phosphatases, modulation of opioid receptor internalization/trafficking, and modulation of protein kinase C (PKC) activity on opioid-induced spinal release of excitatory amino acid release.

Many substances have been shown to block or reverse opioid antinociceptive tolerance. A partial list may include substance *P* receptor (NK-1) antagonists, calcitonin gene-related peptide (CGRP) receptor antagonists, nitric oxide sythase (NOS) inhibitors, calcium channel blockers, cyclooxygenase (COX) inhibitors, PKC inhibitors, competitive and noncompetitive antagonists of the NMDA receptor, AMPA (alpha-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid) receptor antagonists, antidynorphin antiserum, and cholecystokinin (CCK) receptor antagonists (48).

Opioids and NMDA Receptor Antagonists

As the NMDA receptor is believed to play a significant role in opioid tolerance (49,50), COAs of opioids and NMDA antagonists were produced. Unfortunately initial studies with MorphiDex® (morphine sulfate/dextromethorphan hydrobromide combination) in the treatment of chronic pain were disappointing (51).

Activation of mGluR5 may mobilize the release of intracellular Ca (2+) and activate PKC, leading to morphine-induced antinociception suppression (52). Xu et al (52) conclude that mGluR5 contributes to the development of tolerance to morphine-induced antinociception after chronic morphine exposure.

Opioids and Ultra-low Dose MOR Antagonists

Oxytrex (Pain Therapeutics, Inc.) is an oral opioid that combines a therapeutic amount of oxycodone with an ultra-low dose of the antagonist naltrexone (NTX). Animal data indicate that the combination of an opioid with an ultra-low dose of a MOR antagonist may minimize the development of physical dependence and analgesic tolerance while promoting analgesia (53).

To evaluate the safety and efficacy of the oxycodone/naltrexone combination, 3 clinical studies have been conducted, 1 in healthy volunteers and the other 2 in patients with chronic pain (54). The putative mechanism of ultra-low-dose naltrexone is to prevent an alteration in G-protein coupling by opioid receptors that is associated with opioid tolerance and dependence (54). Opioid agonists are initially inhibitory, but may become excitatory through constant opioid receptor activity (54). The agonist/antagonist combination of Oxytrex may reduce the conversion from an inhibitory to an excitatory receptor, thereby decreasing the development of tolerance and physical dependence (54).

Nociceptive types of DRG neurons in culture showed that exogenous GM1 rapidly increased the efficacy of excitatory (Gs-coupled) opioid receptor functions (55). Treatment of DRG neurons with the nontoxic B-subunit of cholera toxin (CTX-B) which binds selectively to GM1, blocked the excitatory, but not inhibitory, effects of morphine and other bimodally-acting opioid agonists, thereby resulting in a net increase in inhibitory opioid potency (55). Shen and Crain (55) suggested that chronic cotreatment of mice with morphine plus CTX-B attenuates the development of opioid tolerance and physical dependence, as previously shown to occur during cotreatment with low-dose NTX.

The endogenous glycolipid GM1 ganglioside, which plays a critical role in nociceptive neurons via regulating opioid receptor excitatory signaling, contributes to "paradoxical" morphine hyperalgesia and to opioid tolerance/dependence. Neuraminidase (sialidase) increases levels of GM1, a monosialoganglioside, in these neurons by enzymatic removal of sialic acid from abundant polysialylated gangliosides. Crain and

Shen (56) demonstrated that acute treatment of mice with the neuraminidase inhibitor, oseltamivir, enhanced morphine analgesia. Acute administration of oseltamivir also reversed "paradoxical" hyperalgesia induced by an extremely low dose of morphine, thereby unmasking potent analgesia. In chronic studies, coadministration of oseltamivir, with morphine prevented and reversed the hyperalgesia associated with morphine tolerance (56). These results provide the first evidence indicating that treatment with a neuraminidase inhibitor, oseltamivir, blocks morphine's hyperalgesic effects by decreasing neuronal levels of GM1 (56).

Combining ultralow doses of micro- or delta-receptor antagonists (e.g., naltrindole) with spinal morphine augmented the acute analgesic effects, inhibited the induction of chronic tolerance, and reversed established tolerance (57).

Opioids and CCK Receptor Antagonists

CCK is believed to play a significant role in the rostral ventral medulla (RVM) in mediating OIH tolerance (58). Prolonged opioid exposure enhances a descending pain faciliatory pathway from the RVM that is mediated at least in part by CCK activity and contributes to the maintenance of antinociceptive tolerance (48). 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 (59). Thus, IT 5-HT3 receptor antagonists or IT NK-1 antagonists may be beneficial to future therapeutic options if proved to be safe intrathecally to use in conjunction with long-term opioid therapy.

Interestingly, 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 (60).

Opioids and Beta Blockers

Liang et al (61) administered the selective beta 2 adrenergic receptor (β2-AR) antagonist butoxamine in β2-AR knockout mice along with or after morphine. Physical dependence was assessed using naloxone-precipitated withdrawal. The expression of CGRP and substance *P* were measured in spinal cord and DRG tissues using both real-time PCR and enzyme-linked immunoassay and revealed that both the coadministration of butoxamine with morphine and the administration of butoxamine after chronic morphine reversed morphine tolerance. Morphine failed to cause tolerance in β2-AR knockout mice. Physical dependence was reduced under the same circumstances. The chronic administration of butoxamine with morphine reduced or eliminated the normally observed up-regulation of CGRP and substance *P* in spinal cord and DRG tissues. The results of Liang and colleagues suggest that the β2-AR modulates both opioid tolerance and physical dependence. Activation of β2-ARs appears to be required for some of the key neurochemical changes which characterize chronic opioid administration. Therefore, β2-AR antagonists may show some promise as agents to enhance chronic opioid analgesic therapy (61).

Opioids and IT NK-1 Antagonists or Serotonin Receptor Antagonists

Although NK-1 antagonists and 5HT-3 receptor antagonists should not be utilized intrathecally at this point in time, hypothetically they may possess future utility for certain painful conditions, especially in combination with opioids. IT 5-HT-3 receptor antagonists (62) 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). While NK-1 receptor internalization was observed primarily in the superficial laminae of placebo-treated rats, NK-1 receptor internalization was seen in both superficial and deep lamina of the DH in morphine-treated animals (63). Morphine-induced hyperalgesia was reversed by spinal administration of an NK-1 receptor antagonist in rats and mice, and was observed in wildtype (NK-1[(+/+]), but not NK-1 receptor knockout (NK-1[(-/-)], mice (60). Spinal NK-1 receptor expressing neurons appear to contribute to mediating OIH and antinociceptive tolerance via activation of descending facilitatory pathways (63,64).

Opioids and Other Agents

Joshi and colleagues (65) studied the possible reversal of morphine-induced tolerance and dependence by bupropion in mice. Chronic administration of bupropion (2 or 5 mg/kg) during the induction phase (days 1-9) (of a 10-day repeated injection of morphine regimen) delayed the development of tolerance to the antinociceptive action of morphine, also reversed naloxone (2 mg/kg) on day 10, i.e., during the expression phase of morphine dependence, and reduced the incidence of naloxone-precipitated withdrawal jumps without affecting tolerance to the analgesic effect (65). Joshi et al (65) concluded that the results suggest the potential beneficial use of bupropion in tolerance and dependence.

Shu et al (66) found that processed Aconiti tuber (PAT) could inhibit morphine tolerance in mice. Mice received subcutaneous (sC) morphine (10 mg/kg) and oral PAT at a subanalgesic dose (0.3 g/kg), once a day for 12 days. Results of the study suggested that chronic treatment with PAT at a subanalgesic dose maintained MOR-mediated morphine antinociception by attenuating development of morphine tolerance, and that this tolerance-attenuating effect of PAT was mediated by the kappa opioid receptor (KOR) (66).

IT bovine adrenal medulla 22, an endogenous opioid peptide, partially reverses morphine tolerance (67). However, its mechanism remains unclear. Cai et al (68) studied the effects of BAM8-22, a derivative of BAM22 and selective sensory neuron-specific receptor (SNSR) agonist, on the development and maintenance of tolerance to spinal morphine (68). Coadministration of BAM8-22 (0.1 nmol) every other day, but not daily, with morphine remarkably attenuated the development of morphine tolerance. Pretreatment and cotreatment with BAM8-22 (0.1 nmol) significantly reversed established morphine tolerance. Furthermore, intermittent administration of BAM8-22 with morphine consistently resumed morphine-induced antinociception (68). Cai and colleagues (68) suggested that intermittent SNSR agonists may be able to modulate the sensitivity of opioid receptors serving as a most probable underlying mechanism for the effects of BAM8-22 on morphine tolerance.

Haghparast and colleagues (69) investigated the influence of repeated administration of nicotine on the development of morphine tolerance and dependence. The data suggested that the inhibitory effect of nicotine on morphine tolerance and dependence is mediated by central nicotinic receptors and there is a cross-dependence between nicotine and morphine.

Cahill et al (70) evaluated the ability of chronic IT infusion of NGF to reverse neuropathic pain symptoms and to restore morphine's effectiveness in an animal model of neuropathic pain. Seven days after sciatic nerve constriction injury, IT NGF was administered by continuous infusion (125 ng/µl/h) via osmotic pumps attached to chronically implanted IT catheters (70). Although IT morphine became relatively ineffective with respect to antinociception in this animal model of pain, morphine substantially attenuated the neuropathy-induced warm and cold hyperalgesia, as well as tactile allodynia, in neuropathic rats chronically infused with IT NGF (i.e., IT NGF restored morphine antinociceptive effectiveness) (70). Additionally, it was demonstrated that IT morphine-induced antinociception was augmented by a CCK antagonist in animals chronically infused with IT antibodies directed against NGF (70). Cahill and colleagues (70) hypothesized that NGF is critical in maintaining neurochemical homeostasis in the spinal cord of nociceptive neurons, and that supplementation may be beneficial in restoring and/or maintaining opioid analgesia in chronic pain conditions resulting from traumatic nerve injury (70).

McNaull et al (71) administered 3 IT injections of morphine (15 mcg) in adult rate, at 90 minute intervals, and produced a significant decline of the antinociceptive effect and loss of agonist potency in both the TF and paw-pressure tests. These reduced responses, indicative of acute tolerance, were blocked by coinjection of morphine (15 microg) with naltrexone (NTX, 0.05 ng), D-Phe-Cys-Try-D-Orn-Thr-Pen-Thr-NH2 (CTAP, 0.001 ng), naltrindole (0.06 ng), or nor-binaltorphimine (0.1 ng) (71).

The results support the notion that ultra-low doses of opioid receptor antagonists block acute tolerance to morphine. This effect may result from blockade of opioid excitatory effects that produce a latent hyperalgesia which then contributes to induction of tolerance. The sustained antinociception produced by combination of morphine with an opioid receptor antagonist appears to show dependency on adenosine receptor activity (71). Furthermore, the development of combined opioid-adenosine receptor modulators (with less development of tolerance) may be useful in the future.

6. Combinations to Combat Dependency Issues/Addiction Potential/Craving Sensations

In addition to hypothetical future agents such as morphofen, many other agents may have utility in diminishing opioid-induced craving sensations/dependency issues.

Opioids and NPFF

Neuropeptide FF (NPFF) has been described as an antiopioid peptide. It is believed to play a role in opioid antinociception, dependence, and tolerance. Previous study has indicated that 1DMe ([D-Tyr^1, (NMe)Phe^3]NPFF), a stable analog of NPFF, inhibits acquisition of the rewarding effect of morphine but not of ethanol in mice (72). The rewarding effects of

these drugs were measured in the unbiased paradigm of conditioned place preference (CPP). Kotlinska et al (73) examined the influence of NPFF on the expression of morphine- and ethanol-induced CPP in the biased procedure in rats. NPFF, given ICV at the doses of 5, 10, and 20 nmol, inhibited the expression of morphine-induced CPP, but was unable to inhibit the expression of ethanol-induced CPP (73). Kotlinska and colleagues (73) suggested that NPFF is involved in the expression of morphine reward and felt that their data also further supported an antiopioid character of this peptide.

Opioids and NR2B Subunit-selective NMDA Antagonists

Ifenprodil is a conantokin variant derived from cone snail venom and an NR2B-selective NMDA receptor antagonist which inhibits naloxone-induced withdrawal jumping in morphine-dependent mice (74). Morphine-induced rewarding effects were dramatically suppressed by cotreatment with the NR2B subunit-containing N-methyl-D-aspartate (NMDA) receptor antagonist ifenprodil. Kato et al (75) proposed that the NR2B subunit-containing NMDA receptor may be involved in the rewarding effect of morphine.

Opioids and Glial Inhibitors

Glial cells have been shown to contribute to and/or facilitate various pain states (76). 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 (77). Hutchinson et al (77) demonstrated that selective acute antagonism of TLR4 (e.g., by (+) and (-) isomer opioid antagonists) may lead to palliation of neuropathic pain and potentiation of opioid analgesia. Moreover, activated glia may contribute to opioid tolerance as well as opioid addiction.

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 (78). 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 to rats injected with morphine alone (78).

Furthermore, to check for a link between glia and morphine addiction, Watkins et al (76) tested whether blocking morphine's effects on glial cells would suppress morphine's rewarding effects and thus, reduce opioid craving sensations. Animals receiving morphine alone tended to return to the morphine area over and over, spending most of their time there. However, rats also given AV-411 in the AV-411-plus-morphine group wandered around randomly rather than returning to the morphine area,thus, demonstrating that glial inhibitors appeared to be able to reduce or eliminate normal opioid-induced reward effects and opioid-induced craving sensations.

Yao et al (79) found that an Adenosine A2a receptor administered either direcly into the NAc or indirectly by IP 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 abstinent heroin addicts. Perhaps Adenosine A2a receptor modulators may be potentially useful agents to combine with opioids and cannabinoids.

Agmatine is an amine that is formed by decarboxylation of L-arginine by the enzyme arginine decarboxylase (ADC) and hydrolyzed by the enzyme agmatinase to putrescine (80). Agmatine binds to several target receptors in the brain and has been proposed as a novel neuromodulator. In animal studies, agmatine potentiated morphine analgesia and reduced dependence/withdrawal (80). While the exact mechanism is not clear, the interactions with N-methyl-D-aspartate (NMDA) receptors, α2-adrenergic receptors, and intracellular cyclic adenosine monophosphate (cAMP) signaling have been proposed as possible targets (80). Like other monoamine transmitter molecules, agmatine is rapidly metabolized in the periphery and has poor penetration into the brain, which limits the use of agmatine itself as a therapeutic agent (80). However, the development of agmatinase inhibitors may offer a useful method to increase endogenous agmatine in the brain as a possible therapeutic approach to potentiate morphine analgesia and reduce dependence/withdrawal (80).

Summary

In general, COAs attempt to maximize the positive or beneficial aspects of opioids and minimize their negative or detrimental effects. Numerous agents may have the potential to modulate various aspects of opioid-induced actions. It remains a surmountable but difficult challenge to assess which of these or other potential future COAs may possess significant clinical advantages to patients and health care providers alike, over various opioids by themselves.

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