Update to Pharmacological Treatment of Pain

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Opioids

Opioids are classified as strong opioids and weak opioids. Functionally, they are grouped according to their intrinsic activity as full agonists, partial agonists, or agonists-antagonists (nalbuphine, naloprhine).

Morphine has a variable oral bioavailability between 10 and 45% (*Table 1*). Its metabolites include morphine-6-glucuronide which causes additional analgesia, and morphine-3-glucuronide (M3G) which cause adverse effects. Controlled release preparations are available. The NNT (numbers-needed-to-treat) for 10 mg morphine for postoperative pain is 2.9[1] and its NNH (numbers-needed-to-harm) is 9.1.

Oxycodone is a semisynthetic derivative of thebaine. It has intrinsic analgesic properties (activation of kappa opioid receptors) and predominantly a prodrug. It is converted to oxymorphone (a mu-opioid agonist) and noroxycodone, an inactive metabolite (*Table 1*). Compared to morphine, it does not have the metabolic issues and appears to be associated with a lower incidence of hallucinations and itching. The oxycodone:morphine ratio is 1:1.5 (*Table 2*). It's NNT of 2.5 in neuropathic pain[2] is comparable to antidepressants. The controlled-release preparation (Oxycontin) has ideal characteristics; there have been reports of abuse from people crushing the preparation.

Hydromorphone, a mu-receptor agonist, is 3 to 5 times more potent than morphine when given orally and 5 to 7 times as potent when given parenterally. Its duration of analgesic effect, at 3-4 hours, is similar to morphine (Table 1). Pruritus, sedation, nausea and vomiting occur less frequently compared to morphine.[3] Its metabolite, hydromorphone-3-glucoronide (H3G) lacks analgesic property but has neuroexcitatory properties similar to M3G.

Methadone has a good bioavailability (60-95%), high potency, and a long duration of action. It lacks an active metabolite, is inexpensive, and has salutary effects (NMDA receptor antagonist and serotonin reuptake inhibitor).[4] It's potency compared to morphine ranges from 1:1 to 1:4 (Table 2). Its unpredictable half-life increases the risk of accumulation and the need for careful dosing. It is ideal in patients with renal failure since it does not accumulate in these patients. An **FDA Alert advisory** was issued on 11/2006 on death, narcotic overdose, and cardiac arrythmias from methadone. Serious side effects may occur because methadone may "build up in the body to a toxic level if it is taken too often, or if is taken with certain other medications or supplements." The cardiac arrythmias include QT prolongation and Torsades de Pointes. Most reports are based on high dose maintenance (>120 mg) for the treatment of addiction, however QT prolongation can occur with concomitant drugs that inhibit cytochrome P450.

Meperidine has side effects including anticholinergic effects, high lipophilicity which induces drug-seeking behavior, and its metabolite normeperidine is a CNS stimulant.[5] It is 8-10 times less potent than morphine and has a duration of 2-3 hours.

The weak opioids include codeine, hydrocodone, propoxyphene, and tramadol. Codeine is transformed to morphine, via the enzyme cytochrome P450 2D6, and has an NNT of 16.7.[1,6] Some (9%) of white people do not have the enzyme and do not experience analgesia from codeine. Hydrocodone reaches peak serum concentrations within 1 to 2 hours and has a half-life of 2.5 to 4 hours.

Propoxyphene, a synthetic opioid structurally related to methadone, has an NNT of 7.7 for 65 mg and 2.8 for 130 mg.[7] The d-isomer, dexctropropoxyphene, is a non-competitive NMDA antagonist.[8] The serious side effects associated with excessive use of propoxyphene include seizures, cardiac dysrythmias, and even heart block. Its active metabolite, norpropoxyphene, has a weak opioid activity and may cause convulsions.

Tramadol is an opioid agonist and a monoaminergic drug. It has a high bioavailability (80-90%) and a dose dependent analgesic efficacy with NNTs of 8.5 for 50 mg, 5.3 for 75 mg, 4.8 for 100 mg, and 2.9 for 150 mg.[1] Maximum dose is 600 mg per day. Its risk of fatal respiratory depression is minimal and possibly limited to patients with severe renal failure, it has a low abuse potential, and the incidence and severity of constipation is less.

Opioid rotation. Opioid rotation or substitution is employed to improve analgesia and decrease side effects. The rationale for this practice includes incomplete cross-tolerance, differences in individual receptor binding, and differences in pharmacokinetics and activity of some of the metabolites. Opioid rotation implies knowledge of the equianalgesic dosages of the different opioids (*Table 2*).

Table 1. Selected Opioids: Oral Bioavailability, Half-lives, Duration of Action, & Metabolites
M6G: morphine-6-glucuronide; M3G: morphine-3-glucuronide; H3G: hydromorphone-3-glucuronide; O3G: oxymorphone-3-glucuronide

Opioid	Availability (%)	½ life (h)	Duration (h)	Metabolites
Morphine	10-45	2-3	4-5	M6G, M3G
Oxycontin	60-80	4.5	12	Oxymorphone Noroxycodone
Oxymorphone (Opana ER^{R})	10	9 +/- 3	12	O3G 6-OH-oxymorphone
Hydromorphone	24	2.3	3-4	H3G
Methadone	60-95	8-80 (27)	6-8	

Table 2. Equianalgesic dose of opioids

Equianalgesics Doses of Opioids	
Opioid	Oral equianalgesic dose (mg)
Morphine	10
Meperidine	100
Oxycodone	7.5
Hydromorphone	2
Methadone	10-20
Oxymorphone	1.5
Hydrocodone	10
Codeine	80
Tramadol	40
Propoxyphene	43-45

Tables 1 and 2 are adapted from Benzon HT, Rathmell JP, Wu CL, Turk DC, Argoff CE (Eds). *Raj's* Practical Management of Pain 4th Ed. New York: Elsevier-Mosby, 2008 (in press).

Side Effects. Two drugs in late stage of development counteract the opiate-induced inhibition of GI motility. Methylnaltrexone (MNTX, Progenics Pharmaceuticals/Wyeth) is given IV and works directly in the GI tract; several studies showed its efficacy in reversing the GI effects of opioids.[9,10] Alvimopan (Adolor/Glaxo can only be given orally, it has been studied for opiate induced bowel dysfunction and for prevention of postoperative ileus.[11,12]

Opioids and driving performance. Patients on stable doses of morphine (up to 290 mg) have selective effects on cognitive function which are considered non-hazardous with regards to driving abilities.[13,14] Patients on stable doses of transdermal fentanyl over 2 weeks show no significant psychomotor impairment.[15] However, patients who have dose increments >30% in the past 2 days show worsening of their cognitive performance.[16] It appears that it is acceptable to let patients drive while on stable doses of opioids but patients who are being initiated on opioid therapy and those who are having dose escalations greater than 20% should be warned about driving.

Efficacy of opioids in different chronic pain syndromes (*Table 3*):
Cancer pain. Long-acting opioids are generally preferred supplemented by short-acting analgesics for breakthrough pain.[17] Opioid monotherapy is rarely successful so adjunctive treatments (medical and nonmedical) should be used whenever possible; interventional procedures should be used whenever appropriate.
Low back pain. Patients with LBP who are prescribed opioids are more likely to have greater disability, greater distress and suffering, and have neurologic signs.[18,19] While individual studies showed the efficacy of opioids in LBP, a meta-analysis did not show reduced pain when compared to a placebo or a nonopioid control group.[20] The different opioids demonstrated a nonsignificant reduction from baseline; opioids may be efficacious for short-term

relief and that long-term efficacy (≥ 16 weeks) is unclear.[20] The available evidences support the effectiveness of NSAIDs in acute and chronic LBP, muscle relaxants in acute LBP, and of antidepressants in chronic LBP.[21]

Neuropathic pain. Recent studies showed some efficacy of opioids.[22-24] Short-term studies provide only equivocal evidence while intermediate-term studies demonstrate efficacy of opioids over placebo.[25] Higher doses may be required resulting in intolerable side effects.[26] The regulatory issues, addiction, and aberrant behaviors associated with opioids make it a second-line drug for neuropathic pain. The combination of a gabapentin and an opioid has been shown to result in better analgesia, less side effects, and lower doses of each drugs.[27]

Fibromyalgia. Tramadol[28] or tramadol/acetaminophen[29] combination has been shown to be more effective than placebo. The side effects were minor and discontinuation of the drug due to side effects was not significantly different between tramadol and placebo.

Spinal cord injury (SCI). Intravenous alfentanil was shown to be better than placebo while IV or intrathecal morphine was not; intrathecal morphine/clonidine was better than placebo.[30]

Table 3. Efficacy of opioids in chronic pain

Chronic pain	Efficacy	Note(s)
Cancer pain	Efficacious	Long-acting opioid recommended, short-acting for breakthrough; adjuvants recommended; interventional procedures as appropriate
Low back pain	Efficacious	Short-term treatment recommended; long-term efficacy (≥ 16 weeks) not determined; NSAIDs, muscle relaxants, antidepressants as appropriate
Neuropathic Pain	Efficacious	Equivocal short-term efficacy; intermediate efficacy better than placebo; second-line drug; combination with anticonvulsant recommended
Fibromyalgia	Efficacious	Only tramadol studied
Spinal cord Injury	Not efficacious	IV alfentanil better than placebo; IV or intrathecal (IT) morphine not better than placebo; IT morphine/clonidine better than placebo; No study on oral opioid

Anticonvulsants

The anticonvulsants block sodium channels; act on ion channel systems including $GABA_A$ receptor agonists (topiramate and felbamate), $GABA_A$ transaminase blockers (vigabatrin), $GABA_A$ transport blockers (tiagabine),and glutamate receptor antagonists (felbamate and topiramate); and block calcium channels (lamotrigine), T-type calcium channels (topiramate and zonisamide), and alpha-2-delta subunits (gabapentin and pregabalin).

Gabapentin has few side effects and lacks drug-drug interactions, median effective dose is 900-1800 mg a day. It has been shown to be effective in PHN, DPN, and SCI.[1-3] Pregabalin has an improved linear pharmacokinetic profile. It has been shown to be effective in PHN, DPN, and SCI pain.[5-8] The maximum dose of pregabalin is 600 mg per day in patients with creatinine clearance (CrCL) > 60 mL/min or 300 mg in patients with CrCl of 30-60 mL/min.

Lamotrigine has been shown to be effective in HIV polyneuropathy, pain from SCI, and central post-stroke pain (CPSP).[9-11] The most common side effect is rash, this is increased in patients taking valproate. Topiramate was found not to be effective in DPN but was effective in migraine prophylaxis, [12-14] divalproex is also effective in migraine prophylaxis.

Oxcarbazepine is similar in chemical structure to carbamazepine but with a different metabolism. It is effective in trigeminal neuralgia with few side effects,[15,16] the pain relief is noted within 24-48 hours. Some patients who are unresponsive to carbamazepine may respond to oxcarbazepine.

The side effects of anticonvulsants include dizziness, fatigue, somnolence, weight gain, peripheral edema (gabapentin & pregabalin); rash (lamotrigine); paresthesia, cognitive effects, weight loss (topiramate); hyponatremia & low thyroid concentrations (oxcarbazepine).

Antidepressants

The mechanisms of analgesic effects of the TCAs include a serotonergic effect (interference with serotonin reuptake and alteration of serotonin binding to receptors),[1] noradrenergic effect, opioidergic effect,[2] effect on the NMDA (blockade, binding to the NMDA receptor complex)[3] and adenosine receptors (inhibition of uptake of adenosine), and blockade of the sodium and calcium channels. TCAs also inhibit the histaminic, cholinergic muscarinic and

nicotinic receptors resulting in sedation, dry mouth, and urinary retention.[4] The NNTs of antidepressants are comparable to opioids and anticonvulsants (*Table 4*).

Amitriptyline,[5] nortriptyline,[6] and desipramine[7] have been shown to be effective in PHN. Nortriptyline and amitriptyline are both effective in PHN but that nortriptyline has fewer side effects.[5] For DPN, amitriptyline and desipramine appear to be equally effective[8] while clomipramine appears to be better than desipramine.[9]

Selective Serotonin Reuptake Inhibitors (SSRIs): The antinociceptive effect of SSRIs appears to involve serotonergic as well as opioidergic (e.g. paroxetine) systems. IN DPN, SSRIs, specifically fluxetine, appears to be less effective than amitriptyline or desipramine.[8] SSRIs appear to be of little benefit in fibromyalgia.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs): SNRIs block the reuptake of serotonin and norepinephrine, with duloxetine and venlaflaxine having increased selectivity for serotonin. Venlafaxine and duloxetine have been shown to have an analgesic effect in the nerve constriction model of neuropathic pain.[10] Duloxetine is effective in DPN and in fibromyalgia[11,12] while venlafaxine is effective in fibromyalgia.[13]

Driving performance. TCAs impair driving ability during the first week of therapy or during dose escalation but driving performance returns to baseline after that .[14] No impairment of driving ability occurs with SSRIs.[15]

Neuropathic pain: Comparative efficacy of anticonvulsants, opioids, and antidepressants
Finnerup[16] noted that for peripheral neuropathic pain, the lowest NNT was for TCAs, followed by opioids and the anticonvulsants gabapentin and pregabalin. If pain relief is the only criteria, then their recommended order of drugs were TCA > opioids $\geq$ tramadol $\geq$ gabapentin/pregabalin. If the criteria are based on pain relief and quality of life, then their recommended order of drugs were gabapentin/pregabalin > tramadol > opioids > TCA.

Local anesthetics: Lidocaine patch, Local anesthetic infusions, Mexilitine
Lidocaine patch contains 700 mg of lidocaine mixed with an adhesive, most patients experience pain relief within few days of application[1] while some have a delayed response.[2] Some patients continue to experience relief between patch applications while others have pain when the patch is removed. In these patients, the patch may be used for 16-18 hours. Only 3% ± 2% of the total dose applied is absorbed systemically.[3] Studies in patients with PHN showed the patch to be more effective than a placebo patch or no treatment.[2,4]

The median dose of intravenous lidocaine infusions is 5 mg/kg given over 30 minutes. A meta-analysis showed IV lidocaine to be superior to placebo and equal to morphine, gabapentin, and amitriptyline for neuropathic pain.[5] The beneficial effect was noted to be more consistent in patients with peripheral pain secondary to trauma and diabetes and in central pain. The median dose of mexiletine is 600 mg per day. Its efficacy is similar to IV lidocaine although favorable response to IV lidocaine does not necessarily mean response to mexiletine.

Table 4. Numbers-Needed-to Treat (NNT) of the Different Drugs

Drugs	Numbers-Needed-to-Treat (NNT)(NNH)	Numbers-Needed-to-Harm
Opioids	2.1 – 3.8	9
Anticonvulsants	2.9 (DPN); 3.9 (PHN)	3.7 (minor event); NS (major event)
TCAs	2.0 – 2.8 (PHN); 1.3 – 3.4 (DPN); 1.7 (CP)	4.5 (minor); 16 (major adverse event)
SSRIs	6.7 ; 5 (paroxetine); 15.3 (fluxetine)	21-24
Lidocaine patch	4.4	---

Which drug(s) to use? Based on original studies, review articles, and meta-analyses publications, the recommended drugs for the different chronic pain syndromes are listed on *table 5*.

Table 5. Recommended drugs for the different chronic pain syndrome

PHN	DPN	SCI	Fibromyalgia	HIV
Pregabalin	Duloxetine	Pregabalin/	Duloxetine	Lamotrigine
Gabapentin	Pregabalin	Gabapentin	Tramadol	
Opioid	Gabapentin	Lamotrigine	Pregabalin	
Antidepressants	Antidepressants	IV lidocaine	Na Oxybate	
Tramadol		Mexilitine (+/-)		
Lidoderm patch (allodynia)				

Drugs for the interventional physician

Steroids. Reports of CNS injuries after TF ESI include paraplegia and cerebral embolism.[1,2] The mechanisms include occlusion of the feeder vessels to the spinal cord secondary to trauma, spasm, or from the particulate steroid; and, embolization of the particulate steroid via the vertebral artery or the feeder vessels to the spinal cord. The susceptible arteries are in close proximity to the cervical intervertebral foramina and can be injured during TF injections.[3] Studies[4,5] noted that methylprednisolone had the largest particles, betamethasone had the smallest particles followed by triamcinolone.[5] Dexamethasone is in liquid form and has a long duration of action.[5] However, a study on its efficacy was preliminary.[6] The depot steroids have preservatives and vehicles that have allergic or neurotoxic implications (*Table 6)*.[5]

Table 6. Comparison of the Different Steroids in Terms of Glucorticoid Potencies, Component Vehicles, and Preservatives

		Vehicle	Preservatives		
Steroid	Relative Glucocorticoid Potency†	PEG	Benzyl Alcohol	Methyl-paraben	Sodium Bisulfite
Methylprednisolone	5	+	+	-	-
Triamcinolone	5	+/-*	+	-	-
Betamethasone	33	-	-	-	-
Dexamethasone	27	-	-	+	+

PEG: polyethylene glycol † = relative to 1 mg of hydrocortisone

*Triamcinolone acetonide does not contain PEG while triamcinolone diacetate does.

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