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Update on the Pharmacological Management of Chronic Pain

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Opioids

Morphine has a variable oral bioavailability between 30 and 65% (table 1). Its metabolites include morphine-6-glucuronide which causes additional analgesia, and morphine-3-glucuronide (M3G) which cause adverse effects. Its hydrophilicity results in the delay in its transport across the blood-brain barrier, slower onset of action, and longer analgesic effect (4-5h) relative to its plasma ½ life (2-3.5h). This result in less accumulation and improved safety.[1] Its metabolism is via the liver end excretion of its metabolites are through the kidneys.

Oxycodone has intrinsic analgesic properties (activation of kappa-opioid receptors) and is predominantly a prodrug. It is converted by the enzyme cytochrome P450 2D6 to oxymorphone and noroxycodone, an inactive metabolite. Ten % of the population has lower levels of the enzyme resulting in lower concentrations of the oxymorphone and higher dosages are required to obtain relief. It has no ceiling dose, minimal side effects, minimal active metabolite, rapid onset of action, long duration of action, & predictable pharmacokinetics.[2] It has a more predictable and slightly higher bioavailability (>50%) (table 1) than morphine. The oxycodone:morphine ratio is 1:1.5.

Hydromorphone 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. H3G is produced in small quantities explaining the relative absence of neuroexcitatory symptoms.

Oxymorphone is available in an immediate and slow-release preparation (Opana^{R}). It has great affinity for the mu- and delta opioid receptors with little affinity for the k-opioid receptor.[4,5] It causes less histamine release compared to morphine.[6] It's bioavailability is only 10% due to extensive first-pass hepatic metabolism. Steady-state occurs after 3 days of BID dosing. There is minimal interaction with cytochrome P450 enzymes resulting in less interpatient variability and fewer drug-drug interactions. Alcohol combined with oxymorphone has been shown to result in an almost 300% increase in the plasma concentration of the drug.[5]

Table 1. Selected Opioids: Oral Bioavailability, Half-lives, Duration of Action, & Metabolites

Opioid	Availability (%)	½ life (h)	Duration (h)	Metabolites
Morphine	30-65	2-3	4-5	M6G, M3G
Oxycontin	60-80	4.5	12	Oxymorphone Noroxycodone
Hydromorphone	24	2.3	3-4	H3G
Oxymorphone	10	9 +/- 3	12	O3G 6-OH-oxymorphone
Methadone	60-95	15-60 (22)	6-8	

M6G: morphine-6-glucuronide; M3G: morphine-3-glucuronide; H3G: hydromorphone-3-glucuronide; O3G: oxymorphone-3-glucuronide
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Methadone has 60-95% bioavailability, high potency, and a long duration of action. Its potency compared to morphine ranges from 1:1 to 1:4. Its unpredictable half-life (15 to 60 hours, mean of 22 hours) increases the risk of accumulation and the need for careful and individualized dosing. The rates of metabolism of methadone vary greatly

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between individuals.[7] The cardiac arrythmias include QT prolongation (see Box 1), occurring mostly in patients on high dose maintenance (>120 mg) for the treatment of addiction.[8] A third of fatal methadone overdoses were in patients who were prescribed methadone.[9] Guidelines for its use include elicitation of history of heart disease or arrhythmia, disclosure of the risk of arrhythmia from methadone, screening pre-ECG, follow-up ECG within 30 days and annually especially for doses greater than 100 mg/day.[10]

Box 1: Criteria for Normal, Borderline and Prolonged QTc Intervals

QTc (msec)	Male	Female
Normal	<430	< 450
Borderline	431-450	451-470
Prolonged	>450	>470

Recommendations based on QTc intervals:[10]
QTc interval 450-500 ms: discuss risks
>500 ms: reduce methadone dose or discontinue

Hydrocodone has a serum ½ life of 3.8 hours and is metabolized by the liver; it has strong anitussive properties similar to codeine. Many pharmaceutical products combine hydrocodone and nonopioid analgesics specifically acetaminophen, these combination products have been shown to cause psychomotor impairment in volunteers.[11] The abuse potential of hydrocodone appears to be similar to oxycodone and is dose-related.[12]

Codeine is transformed to morphine, via the enzyme cytochrome P450 2D6, and has an NNT of 16.7. Nine percent of Caucasians do not have the enzyme and do not experience analgesia from codeine.[13] Children less than 12 years of age lack maturity of the enzyme and cannot convert the drug to morphine, experiencing the drug's side effects with minimal analgesia.[14] Studies showed that some Asians, specifically the Chinese, also lack the enzyme.[15]

Tramadol is an opioid agonist and a monoaminergic drug. It has a high bioavailability (80-90%) and a dose dependent analgesic efficacy. An issue is its association with seizure activity, although occuring in less than 1% of users, especially in patients with a history of alcohol abuse, renal insufficiency, stroke, and head injury. Patients who are on SSRIs should probably not take tramadol because of the risk of development of serotonin syndrome. The syndrome is chracterized by the triad of neuromuscular and autonomic hyperactivity, and altered mental status.[16]

Side Effects: For constipation, methylnaltrexone (Relistor^{R}) is given subcutaneously and works directly in the GI tract. It appears to be effective in reversing the GI effects of opioids.[17] Alvimopan (Adolor^{R}) is given orally and has been studied for opiate induced bowel dysfunction and for prevention of postoperative ileus.[18,19] Opioids affect the HPA axis and the hypothalamic-pituitary-gonadal axis, causing a decrease in testosterone, estrogen, cortisol, luteinizing hormone, and follicle-stimulating hormone, and an increase in prolactin. These disturbances can lead to amenorrhea, irregular menses, galactorrhea, decreased libido, and osteoporosis.[20] Opioids may alter the development, differentiation, and function of immune cells. Repeated administration of opioids may result in opioid-induced hyperalgesia. A possible mechanism involves neuroplastic changes in both the peripheral and central nervous systems leading to sensitization of pro-nociceptive pathways.[21]

Opioids and driving performance: Stable doses of morphine of up to 290 mg are considered non-hazardous with regards to driving abilities.[22] Patients on stable doses of transdermal fentanyl over 2 weeks show no significant psychomotor impairment when compared to volunteers.[23] Patients who have dose increments greater than 30% in the past 2 days show worsening of their cognitive performance.[24] The psychomotor performance and driving ability of patients on opioids (average, 118 mg morphine) and normal volunteer controls were noted to be similar.[25]

Efficacy of opioids in different chronic pain syndromes:

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Opioids are the mainstay of treatment for *cancer pain*.[26] Long-acting opioids are preferred and should be supplemented by short-acting analgesics for breakthrough pain. For *low back pain,* up to 60% of patients are prescribed opioids for LBP.[27] Patients on opioids include those with greater disability, poorer functioning, greater distress and suffering, higher functional disability scores, have neurologic signs, dermatomal pain distributions, and pain radiation.[28,29] A meta-analysis that compared the efficacy of different opioids demonstrated a nonsignificant reduction from baseline and the authors concluded that opioids may be efficacious for short-term relief but long-term efficacy (≥ 16 weeks) is unclear.[27] For *neuropathic pain.* Studies showed efficacy of opioids,[30,31] short-term studies provide equivocal evidence while intermediate-term studies demonstrate efficacy of opioids over placebo.[32] A placebo-controlled study showed the superiority of morphine over mexiletine in phantom pain.[33] 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.[34] For *fibromyalgia, t*ramadol[35] or tramadol/acetaminophen[36] combination has been shown to be more effective than placebo.

Anticonvulsants

Gabapentin has few side effects (table 2) and lack drug-drug interactions. Median effective dose ranges from 900 to 1800 mg. Gabapentin has been shown to be effective in PHN, DPN, and SCI.[1-3] The combination of gabapentin and morphine was shown to be more effective than either drug alone and at lower dosages.[4] It appears not to effective in post-amputation and phantom limb pain.[5] The combination of gabapentin and nortriptyline was found to be very effective in neuropathic pain from diabetes and varicella zoster.[6]

Pregabalin shares the same mode of action as gabapentin but with a more rapid onset of action, linear pharmacokinetics, fewer dose-related side effects, and BID versus TID dosing. Pregabalin is effective in PHN, DPN, SCI pain, and fibromyalgia.[7-10] In a study on neuropathic pain of different etiology pregabalin was noted to be effective in this broad range of neuropathic pain syndromes.[11] Significant differences were noted in sleep interference, anxiety and depression subscales, and patient satisfaction between pregabalin and placebo.

Lamotrigine has been shown to be effective in HIV polyneuropathy, DPN, and pain from SCI and central post-stroke pain (CPSP).[12-14] It was noted to be effective in patients with trigeminal neuralgia who were not responsive to carbamazepine.[15] The most common side effect is rash, the incidence is increased in patients taking valproate.

Table 2. Side Effects Common Anticonvulsants and Antidepressants

Gabapentin & pregabalin	Dizziness, somnolence, fatigue, weight gain, peripheral edema
Lamotrigine	Rash, Stevens Johnson syndrome
Oxcarbazepine	Hyponatremia, low thyroid concentrations
Topiramate	Weight loss, *cognitive effects*
Valproic acid (Depakote^{R})	Tremor
TCAs	Cholinergic effects (dry mouth, sedation, urinary retention)
Milnacipran	Nausea, headache, constipation

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Antidepressants
The NNTs of antidepressants are comparable to opioids and anticonvulsants (table 3). Amitriptyline, nortriptyline, and desipramine have been shown to be effective in PHN.[1-3] Nortriptyline and amitriptyline are both effective in PHN but nortriptyline has fewer side effects. For DPN, amitriptyline and desipramine appear to be equally effective[4] while clomipramine appears to be better than desipramine.[5] A combination of gabapentin and nortriptyline – two generic medications - was found to be very effective in neuropathic pain from diabetes and varicella zoster.[6] TCAs, but not SSRIs, impair driving ability during the first week or during the dose escalation of the drug but performance returns to baseline after one week. [7,8]

Selective Serotonin Reuptake Inhibitors (SSRIs): The antinociceptive effect of SNRIs appears to involve serotonergic as well as opioidergic (e.g. paroxetine) systems. IN DPN, SSRIs, specifically fluoxetine, appears to be less effective than amitriptyline or desipramine.[4] SSRIs appear to be of minimal benefit in fibromyalgia.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs): SNRIs block the reuptake of serotonin and norepinephrine, with venlaflaxine having increased selectivity for serotonin. Duloxetine has a high and balanced affinity for both norepinephrine and serotonin reuptake transporters.[9] 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]

Milnacipran is an SNRI with a greater selectivity for norepinephrine over serotonin, studies showed it to be effective in fibromyalgia.[13-15] The efficacy of milnacipran in fibromyalgia was noted in terms of fatigue, physical conditioning and discomfort.[13] Salutary characteristics of the drug include its lower affinity for the muscarinic, cholinergic, histaminergic, and alpha-adrenergic receptors, low potential for drug-drug interactions, low protein binding, lack of activity on the cytochrome P450, and limited hepatic metabolism.[15] In a pooled analysis of two RCTs in fibromyalgia, milnacipram, in doses of either 100 mg/day or 200 mg/day, was noted to be superior to be placebo in terms of pain relief, improvement in the SF-36 Physical Component summary scores, and patient satisfaction.[16] The IASPNeuP-SIG and the European FNS now consider the SNRIs as an excellent choice for the treatment of DPN.

Comparison of opioids, anticonvulsants and antidepressants: The NNTs and NNHs of opioids, anticonvulsants, and antidepressants are in table 3.

Table 3. Numbers-Needed-to Treat (NNT) and Numbers-Needed-to-Harm (NNH) of the Different Drugs

Drugs	Numbers-Needed-to-Treat (NNT)	Numbers-Needed-to-Harm (NNH)
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

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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 4.

Table 4. Recommended drugs for the different chronic pain syndrome

PHN	DPN	SCI	Fibromyalgia	HIV Neuropathy	CRPS
Pregabalin	Pregabalin	Pregabalin	Duloxetine	Lamotrigine	Gabapentin
Gabapentin	Gabapentin	Gabapentin	Pregabalin	Gabapentin	Ketamine infusion
Opioid	Duloxetine	IV lidocaine	Milnacipran		
Antidepressants	Antidepressants		Tramadol		
Tramadol					
Lidoderm patch					

Ketamine infusion for CRPS & other chronic pain syndromes: Two randomized double-blind studies showed the efficacy of ketamine infusion in CRPS. In the first study, 60 patients with CRPS I had ketamine infusion at1.2 ug/kg/min (*5mg/h/70 kg*, max: 7.2 ug/kg/min (*30 mg/h/70 kg*) for 4-5 days.[1] There was significant pain relief but it was lost at 12 weeks; there was no functional improvement. The other study showed statistically significant reduction in many pain parameters.[2] In this study, the patients were given ketamine infusion, for 4 hours (25 mg/h) daily for 10 days. The maximum rate of infusion was 0.35 mg/kg/h, not to exceed 25 mg/h; clonidine and midazolam were also given to the patients.[2] The efficacy of ketamine infusion in other chronic pain syndromes was noted in a retrospective study. The infusion was noted to be helpful in patients with CRPS, refractory headaches and back pain; 25-51% relief was noted over 3 weeks.[3] There is a recent report of 3 patients who developed increased liver enzymes and elevated eosinophils after ketamine infusion for CRPS, 10-20 mg/h infusions, two 100-hour infusions, 16 days apart.[4] The accompanying editorial discussed preclinical data about the possible mechanisms of liver toxicity from ketamine.[5]

Prescription Monitoring Programs (PMPs), Risk Evaluation and Mitigation Strategy (REMS). Patients do not adhere to the prescribed regimen, 34% underuse while 14% overuse the medications.[1] A history of substance abuse, especially with multiple substances, is a predictor of opioid misuse.[2,3] A family history of substance abuse, history of legal problems or a mood disorder are significant predictors of aberrant behavior.[2,3] Validated screening questionnaires include the Screener and Opioid Assessment for Patients with Pain (SOAPP),[4] the Opioid Risk Tool,[5] or the Diagnosis, Intractability, Risk, Efficacy (DIRE)[6] may predict aberrant behaviors.

Prescription Monitoring Programs (PMPs) include the collection of prescription data, state controlled processing with data storage, and rules and regulations for those who have access to the data. As of October 2011, all states in the US have either operational or enacted PMP legislation, only Missouri and New Hampshire had pending legislation.[7] There are differences between the PMPs from state to state in terms of data collection methods and the class of drugs that are monitored.[8] The National All Schedules Prescription Electronic Reporting Act (NASPER) provides a source of funding for the states to create and improve prescription drug monitoring databases.[9]

There has been an epidemic of drug abuse and deaths from prescription opioids.[10-12] To decrease drug abuse and overdose, the FDA established Risk Evaluation and Mitigation Strategies (REMS) to "decrease abuse, misuse, addiction, and overdose deaths". Pharmaceutical companies have developed extended-release opioid medications that are difficult to convert into more rapid-acting forms, i.e., "abuse-deterrent formulations". A new tamper resistant formulation of Oxycontin is available, a REMS has been developed by the manufacturer of SR hydromorphone, and a morphine preparation with embedded naltrexone (e.g. Embeda^{R}) has been developed.

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Last year, the White House came out with a document that included goals to tackle the problem.[13] These include the approval and implementation of REMS for certain long-acting and extended release opioids within 12 months, legislation in all 50 states establishing PMPs within 36 months, issuance by the FDA of a guidance document developing abuse deterrent drug formulations and post-market assessment of their performance within 24 months, and a legislation requiring prescribers applying for DEA registration to complete training on the appropriate use, proper storage and disposal of schedule II and III opioids.[13] The central component of REMS is voluntary prescriber education program that will be offered by continuing education providers at no cost to the medical professionals.[14]

Urine Drug Testing (UDT)

Reviewing the results of UDT implies knowledge of drug pharmacology and pharmacokinetics, aspects of urine collection, and understanding the information that was provided.[1] A positive UDT confirms that the patient is taking the prescribed medication. It also informs the clinician whether the patient is taking illicit drugs as long as the drugs are not metabolites of the prescribed medication. A UDT can be negative in a compliant patient who is a fast metabolizer of the drug. UDT cannot be used to estimate blood concentrations or assess efficacy.[1-3]

The blood levels of opioids are affected by absorption, distribution (which is partly dependent on route of administration),[4,5] metabolism and transport of the drug, and receptor affinity.[6-8] The pH of the urine influences the reabsorption and excretion of drugs in the kidney.[9] For example, methadone is excreted at lower urine pH.[1]

Enzyme-mediated immunoassay (EIA) is used for initial evaluation for UDT; EIA has adequate sensitivity but is not specific. It cannot identify a specific opioid/metabolite and can result in false negative result by missing compounds such as oxycodone, methadone, and fentanyl.[10,11] EIA also exhibit cross-reactivity with other drugs (over the counter diet agents and decongestants). Confirmatory testing is usually employed with liquid chromatography/mass spectrometry or gas chromatography/mass spectrometry. With GC/MS or LC/MS, there is no cross-reactivity or false negative results because these methods precisely identify the parent drug and its metabolites. In ordering UDT, the physician should state the drugs that are to be included in the testing and information (name, dose, dosing frequency) about the prescribed medications.

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DISCLOSURE
Pfizer, Consulting Fees