# CO's CURE
# Hospital Medicine Pharmacologic Guidance

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| Acetaminophen | • Evidence: In five randomized controlled trials, acetaminophen significantly lowered pain compared to placebo without increased adverse events. Number needed to treat to achieve pain relief is 4.[1]<br>• Options: Oral, rectal. IV formulations are restricted at many hospitals due to cost (100 times more expensive) and equal efficacy to oral formulations.[2]<br>• Contraindications and cautions: Life-threatening cases of acute hepatic failure leading to liver transplant or death have been linked with acetaminophen use. In most cases of hepatic injury, acetaminophen doses exceeded maximum daily limits and often involved use of more than one acetaminophen-containing product.<br>• Hepatic dosing: In cirrhosis with stable LFTs, reduce total daily dose to 2 grams (expert opinion).[3]<br>• Monitoring: Check liver function tests especially if pre-existing liver disease.<br>• Discharge instructions: Notify patient to avoid other over-the-counter products that contain acetaminophen and limit the total daily dose to less than 4,000 milligrams. |
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| Antidepressants | • Evidence: Duloxetine is noninferior to pregabalin for treatment of pain in patients with diabetic peripheral neuropathy.[4] Duloxetine or tricyclic antidepressants (TCAs) may reduce abdominal pain and increase quality of life in patients with irritable bowel syndrome.[5]<br>• Options: Serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine) and tricyclic antidepressants (amitriptyline, nortriptyline)<br>• Dosing: Dose based on effect and tolerability. Duloxetine: start at 30 mg daily then increase to 60 mg after 1 week. Venlafaxine: start at 75 mg daily then increase by 75 mg every 4 days to 150-225 mg daily. Amitriptyline: start at 10 mg QHS and may titrate up to 50 mg QHS. Nortriptyline: start at 25 mg QHS and increase to 150 mg QHS.<br>• Best use in chronic pain. Do not stop abruptly. It may take up to one week or longer to take effect.<br>• Cautions: SNRIs and TCAS may increase suicide risk in patients 18-25 years old. Do not use concomitantly with MAOIs; do not initiate within 14 days of discontinuation of MAOIs. Avoid TCAs in the elderly (Beer's criteria) due to anticholinergic effects.<br>• Monitoring: For SNRIs, monitor for serotonin syndrome. For TCAs, monitor QTc at baseline and periodically. |
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| Antispasmodics | • Evidence: Cyclobenzaprine reduces low back pain with a number needed to treat of 3.[6] It can also reduce pain scores in patients with renal colic who are receiving NSAIDs, though the difference was not statistically significant.[7]<br>• Antispasmodic options: cyclobenzaprine, tizanidine, methocarbamol, metaxalone. If spasticity (not spasm), consider baclofen.<br>• Dosing: Start at low dose and increase to effect while monitoring sedation.<br>• Mechanism of action: Cyclobenzaprine: acts in the brainstem and reduces tonic somatic motor activity; structurally similar to tricyclic antidepressants. Tizanidine: alpha-adrenergic agonist. Methocarbamol and metaxalone: depresses CNS activity resulting in musculoskeletal relaxation. Baclofen: inhibits transmission of spinal synaptic reflexes.<br>• Contraindications and cautions: Avoid use in elderly patients or patients at increased risk for delirium. All antispasmodics may cause sedation, but anecdotally less sedation is seen with methocarbamol. For tizanidine, may cause bradycardia, hypotension.<br>• Duration of use: Use for shortest possible duration due to sedative side effects. Do not abruptly discontinue baclofen. |
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| Capsaicin topical | • Evidence: May reduce pain in cannabis hyperemesis syndrome, arthritis and neuropathic pain. Evidence is limited.<br>• Mechanism of action: Causes warmth/burning sensation by binding nerve membrane receptors. Initially stimulates then desensitizes and degenerates cutaneous nociceptive neurons; substance P depletion may also reduce pain impulse transmission to the central nervous system.<br>• Contraindications and cautions: May cause burning, redness or pain at the site.<br>• Duration of use: Burning should reduce with repeated administration. May take 1-4 weeks for maximal pain relief. |
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| Desmopressin (DDAVP) | • Evidence: Desmopressin provides comparable pain relief in renal colic to opioids and even more pain relief when added to opioids. No added benefit to NSAIDs.[8]<br>• Dosing: 0.4 mg po daily if NSAIDs are contraindicated. The intranasal formulation can be considered in patients that are unable to take pills.<br>• Mechanism of action: Proposed ureteral smooth muscle relaxation<br>• Contraindications and cautions: Current or history of hyponatremia, polydipsia, von Willebrand disease. Other risk factors for hyponatremia with desmopressin use include cystic fibrosis, renal impairment, heart failure, advanced age and concomitant use of medications known to increase risk of SIADH. Risk of hyponatremia is 1 in 10,000 patients.[14] IV route can be associated with higher risk of thrombo-embolic events.<br>• Monitoring: Check serum sodium prior to initiation. Recheck within one week or sooner if risk for hyponatremia. |
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| Dicyclomine | • Evidence: Beneficial in irritable bowel syndrome.[9]<br>• Mechanism of action: Antispasmodic and anticholinergic that alleviates smooth muscle spasm of the GI tract.<br>• Contraindications and cautions: Avoid use in elderly patients (Beer's criteria) or patients at increased risk for delirium. May worsen urinary retention or ileus. |
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| Gabanoids | • Evidence: 4 out of 10 patients with neuropathy will achieve 50% pain relief with gabapentin.[10]<br>• Options: Gabapentin, pregabalin<br>• Pregabalin has better oral bioavailability and faster onset of action (1 hour vs 3 hours with gabapentin).<br>• Dosing: Initial dose is dependent on renal function, age, and co-morbidities. If sedation is a concern, start initial dose at bedtime. Titrate to effective dose. Do not discontinue abruptly; taper over 1 week.<br>• Contraindications and cautions: Avoid use in older adults (Beers Criteria) with a history of falls as it may cause syncope, impaired psychomotor function or ataxia.<br>• Renal dosing: Adjust dose for renal impairment.<br>• Monitoring: Consider checking serum creatinine.<br>• Discharge: Pregabalin is Schedule V and requires a DEA; may be cost prohibitive. |
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| Haloperidol | • Evidence: Reduces pain intensity and nausea scores in patients with suspected gastroparesis.[11]<br>• Dosing: 1-2 mg Q 4 hrs PRN<br>• Contraindications and cautions: There is a higher risk of QT-interval prolongation and torsade de pointes when administered by IV route or in higher doses. Use caution if treating patients with QT-prolonging conditions, concomitant QT-prolonging drugs and underlying cardiac abnormalities. Use with caution in older adults.<br>• Monitoring: Obtain baseline EKG and repeat periodically during therapy. |
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| Ketamine oral | • Evidence: There is low quality evidence to support use of ketamine for complex regional pain syndrome.[12] Outside the perioperative setting, most studies for acute or chronic pain treatment are small, uncontrolled and either unblinded or ineffectively blinded; also, patient selection, dose and route of therapy differs across studies. Oral ketamine may have a role as add-on therapy in complex chronic pain patients if other therapeutic options have failed.[13]<br>• Mechanism of action: Antagonizes N-methyl-D-aspart (NMDA) receptors in the central nervous system.<br>• Dosing: Average effective dose is 25-50 mg PO Q 4 hrs PRN. Do not exceed 1000 mg PO over 24 hours. Injectable formulation can be used for oral administration and should be mixed with a sweet drink given bitter taste. If concurrent opioids, lower opioid dose prior to starting ketamine to avoid respiratory depression. If used for extended period, avoid abrupt discontinuation and taper dose. Ketamine has reduced oral bioavailability compared to IV administration.<br>• Contraindications and cautions: Avoid use if seizures or non-epileptic seizures, psychosis, mania, dissociative psychiatric disease, history of ketamine abuse, poorly controlled hypertension, heart failure, arrhythmia, increased intracranial pressure (including brain lesion, intracranial bleed), recent stroke, severe respiratory insufficiency or post-traumatic stress syndrome. Ketamine can cause dose-dependent sedation. It is okay for use in patients with depression, anxiety.<br>• Adverse effects: Hypertension, tachycardia, myocardial depression, increased intracranial pressure, vivid dreams, anxiety, hallucinations, tremors, tonic-clonic movements, nausea, sedation<br>• Monitoring: Vitals should be checked 1 hour after initial oral dose, then every 4 hours. If acute change in vitals or intolerable psycho-mimetic effects, stop ketamine and consider benzodiazepine for psycho-mimetic effects.<br>• Discharge: Ketamine is rarely used outside of the hospital and should not be prescribed at discharge. Taper ketamine prior to discharge. Ketamine is a schedule III drug with potential for abuse (date rape drug, special K, etc). |
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| Lidocaine infusions | • Evidence: IV lidocaine was safe for neuropathic pain, better than placebo and as effective as other analgesics.[14] Also shown to improve pain in renal colic and critical limb ischemia compared to morphine in the emergency department.[15,16]<br>• Mechanism of action: Blocks conduction of nerve impulses through inhibition of sodium channels.<br>• Dosing: 1mg/kg/hr. Maximum recommended dose is 120 mg/hr to avoid systemic lidocaine toxicity. If BMI>30, use ideal body weight. Alternative weight-based bolus dosing has been studied for some indications.<br>• Contraindications: Avoid in unstable coronary disease, recent MI, heart failure, severe electrolyte disturbances, cirrhosis, arrhythmia, seizure disorders.<br>• Monitoring: Patients must be on telemetry while on a lidocaine infusion.<br>• Cautions: LAST (local anesthetic systemic toxicity) is a life-threatening adverse reaction. Monitor symptoms below. If concern, stop lidocaine and consider lipid emulsion. A lipid rescue kit should be made readily available in any area of practice that utilizes lidocaine.<br>• Adverse reactions: Early signs of lidocaine toxicity include circumoral numbness, metallic taste in mouth, dizziness, light-headedness or tinnitus. Later signs of toxicity include confusion, slurred speech, blurred vision, myoclonic jerking, seizures. If ongoing undetected or untreated toxicity, can progress to coma, respiratory arrest and cardiovascular effects (hypotension, pulse rate <50 or >120, cardiac arrest).<br>• Recommended duration of use: 24 hours. Longer durations of therapy can be considered but there is increased risk of toxicity. |
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| Lidocaine topical | • Evidence: In myofascial pain, lidocaine patches decrease reported pain compared to placebo.[17]<br>• Options: Patch, ointment, cream, viscous, jelly. Concentrations vary.<br>• Can use up to 3 patches at one time. A small study suggests that it is safe to administer for 24 hours at a time (vs remove after 12 hours) on healthy subjects.[18]<br>• Contraindications and cautions: Only recommended to use on intact skin.<br>• Discharge: If 5% prescription concentration of transdermal patch is cost prohibitive, can prescribe lidocaine 4% patch which is over-the-counter. |
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| Menthol topical | • Evidence: Methyl salicylate and menthol provide significant pain relief of muscle strain compared to placebo.[19] In a small study, menthol was more effective than ice. [20]<br>• Mechanism of action: Stimulates receptors producing cold sensation.<br>• Contraindications and cautions: Recommend use on intact skin. |
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| Non-steroidal anti-inflammatories, systemic | • Evidence: When combined with acetaminophen, can reduce acute pain by 50% in 7 out of 10 patients.[21] Adding an NSAID to a pain regimen containing an opioid may have an opioid-sparing effect of 20-35%.[22] For renal colic, both opioids and NSAIDs lead to clinically relevant reduction in pain scores but opioids have higher rates of adverse reactions, particularly vomiting.[2]<br>• Options: Ibuprofen, naproxen, ketorolac, diclofenac, indomethacin. Selective COX2 inhibitors: Meloxicam, celecoxib<br>• Different side effect profiles: In general, COX2 selective NSAIDs have a lower risk of gastrointestinal side effects but a higher risk of cardiac side effects. Non-selective NSAIDs have a lower risk of cardiac side effects but a higher risk of gastrointestinal side effects.<br>• Contraindications and cautions: NSAIDs increase the risk of myocardial infarction and stroke. Contraindicated in the setting of recent coronary artery bypass graft surgery or myocardial infarction. Can also cause increased risk for gastrointestinal adverse events including bleeding, ulceration and perforation of the stomach or intestines. Risk is especially increased in elderly (Beer's criteria) and in patients with prior peptic ulcer disease or GI bleeding. Caution should also be used in patients on concomitant anticoagulants or antiplatelet agents. Avoid use in patients with chronic kidney disease, cirrhosis or heart failure. Risk of renal injury is higher in patients who are elderly, dehydrated or with other comorbidities including heart failure, diabetes and cirrhosis.<br>• Special considerations: Ketorolac should be limited to 5 days given GI risks. Also, limit ketorolac to 15 mg Q 6 hrs if age >65, wt <50 kg or moderately elevated serum creatinine.<br>• Monitoring: Check serum creatinine and discuss history of GI ulceration prior to initiation.<br>• Recommended duration of use: Use the lowest effective dose for the shortest possible duration. |
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**Figure 1**: Risk of Gastric Ulcer bleeding with NSAIDs [24]

| Individual NSAID | | Adjusted conditional RR (95% CI) |
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| **Low** | **Celecoxib** | 1.0 (0.4-2.1) |
| ↓ | **Ibuprofen** | 4.1 (3.1-5.3) |
| | **Naproxen** | 7.3 (4.7-11.4) |
| | **Indomethacin** | 9.0 (3.9-20.7) |
| **High** | **Ketorolac** | 14.4 (5.2-39.9) |

**Figure 2**: GI risk factor assessment and NSAID therapy (American College of Gastroenterology Guidelines, 2009)[25,26]

| GI risk factor assessment | Treatment |
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| **High Risk**<br>• History of previously complicated ulcer, especially recent<br>• Dual antiplatelet therapy<br>• OR more than 2 risk factors: 1) Age >65 years, 2) high dose NSAID therapy, 3) previous history of uncomplicated ulcer or 4) concurrent use of aspirin, corticosteroids or anticoagulants | Alternative therapy or COX-2 inhibitor + PPI |
| **Moderate Risk**<br>• 1-2 risk factors | NSAID + PPI |
| **Low Risk**<br>• No risk factors | NSAID alone |

*H Pylori is an independent and additive risk factor and needs to be addressed separately.
**Therapeutic anticoagulation is considered an independent factor qualifying for high risk in the 2008 ACCF/ACG/AHA guidelines.

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| Nonsteroidal anti-inflammatories, topical | • Evidence: To achieve 50% reduction in musculoskeletal pain, number needed to treat is 3.7 for topical diclofenac which is about the same for oral NSAIDs.[27]<br>• Options: Diclofenac gel, patch and solution.<br>• Mechanism of action: Only about 5% of topical NSAIDs are systemically absorbed compared to oral NSAIDs but studies show there is local absorption into tissues and synovium.<br>• Contraindications: Similar concerns as oral NSAIDs however a meta-analysis showed systemic adverse events were uncommon and did not differ from placebo.[28]<br>• Consider use in patients who have relative contraindications to systemic NSAIDs.<br>• Discharge: More expensive than oral NSAIDs. |
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| Tamsulosin | • Evidence: Moderate or low quality evidence that it may reduce the time to stone passage and use of pain medications. Sub-analysis shows that benefit might be best for stones 6 mm or larger. Tamsulosin does not influence the need for surgery.[29]<br>• Contraindications and cautions: May cause orthostatic hypotension, complications with cataract surgery and abnormal ejaculation.<br>• Duration of use: Until stone passage. |
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