Pharmacologic Agents Used in the Treatment of Persistent Pain

Indications and Common Uses

Class/Agent	Indication	Common (Off-Label) Use	Level of Evidence
Analgesics, Paraphenol **Acetaminophen**	Treatment of mild to moderate pain		High- Multiple randomized controlled clinical trials for headache and non-neuropathic pain conditions
Analgesics, Topical **Lidocaine patch 5%**	Postherpetic neuralgia	Diabetic neuropathy, osteoarthritis, low back pain	High- Controlled clinical trials for postherpetic neuralgia Moderate- Randomized trial for osteoarthritis; open-label trials for diabetic neuropathy, low back pain
Anticonvulsants **Carbamazepine** **Gabapentin** **Lamotrigine** **Phenytoin** **Pregabalin**	**Carbamazepine:** Trigeminal neuralgia **Gabapentin:** Postherpetic neuralgia **Pregabalin:** Postherpetic neuralgia, diabetic neuropathy	**Carbamazepine:** Postherpetic neuralgia **Gabapentin:** Diabetic neuropathy; other forms of neuropathic pain **Lamotrigine**, **phenytoin:** Some off-label	High- Multiple controlled clinical trials for **gabapentin** and **pregabalin.** **Lamotrigine:** Diabetic neuropathy as add-on to carbamazepine; trigeminal neuralgia and other neuropathic pain conditions
Antidepressants, Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) **Duloxetine** **Venlafaxine**	**Duloxetine:** Diabetic peripheral neuropathic pain **Venlafaxine:** No labeled pain indications	Experimental use for neuropathic pain	Moderate- **Duloxetine:** Some evidence for diabetic peripheral neuropathy (few studies) Low- **Venlafaxine:** Equivocal findings for neuropathy and neuralgia (very limited published data)
Antidepressants, Tricyclic **Amitriptyline** **Amoxapine** **Desipramine** **Doxepin** **Nortriptyline** **Protriptyline**	No indications for pain	Postherpetic neuralgia, phantom limb pain, diabetic neuropathy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis	High- Multiple randomized controlled clinical trials show efficacy in postherpetic neuralgia, peripheral neuropathy, and other chronic pain syndromes

Counterirritants, Topicals, **Capsaicin**	Temporary relief of pain from osteoarthritis, rheumatoid arthritis, postherpetic neuralgia, and diabetic neuropathy	Intractable pruritus, postmastectomy and phantom limb pain	Moderate- Controlled clinical trials with inconsistent findings
COX-2 Inhibitors[*] **Celecoxib** **Rofecoxib**[†] **Valdecoxib**[‡]	Rheumatoid arthritis, osteoarthritis, primary dysmenorrhea		High- Multiple controlled clinical trials
Muscle Relaxants, Centrally Acting **Baclofen**	Orphan drug intrathecally administered. Treatment of intractable spasticity		High- Several randomized controlled trials with spasticity
N-methyl-d-aspartate (NMDA) Inhibitors **Ketamine**	No chronic pain indications	Experimental use only	Low- Very few trials; topical preparation as yet unproven. Some use for breakthrough pain in chronic pain
NSAIDs[*] **Diclofenac** **Ibuprofen** **Naproxen** **Salsalate**	Rheumatoid arthritis, osteoarthritis, primary dysmenorrhea **Ibuprofen:** Acute migraine headache **Diclofenac, naproxen:** Ankylosing spondylitis		High- Multiple randomized, controlled clinical trials for FDA-indicated uses
Opioids, Opioid-like Agents **Tramadol**	Moderate to moderately severe chronic pain		High- Controlled clinical trials for diabetic neuropathy, low back pain, polyneuropathy
Opioids, Oral **Hydromorphone**[†] **Levorphanol** **Morphine** **Oxycodone**	**Oxycodone** and sustained-release preparations of **levorphanol** and **morphine:** Chronic pain		High- Multiple controlled clinical trials: **Levorphanol** specifically for neuropathic pain, **oxycodone** for diabetic neuropathy
Opioids, Transdermal **Fentanyl Transdermal System**[§]	Management of chronic pain in patients requiring continuous opioid analgesia		High- Multiple controlled clinical trials for chronic pain

Sites/Modes of Action and Safety

Class/Agent	Site/Mode of Action	Side Effects/Tolerability
Analgesics, Paraphenol **Acetaminophen**	Inhibits synthesis of prostaglandins in the central nervous system. Peripherally blocks pain impulse generation	Well tolerated Safety concerns: Renal and/or hepatic dysfunction (may be irreversible) with chronic use
Analgesics, Topical **Lidocaine patch 5%**	Peripherally blocks neuronal permeability to sodium ions preventing depolarization and conduction of impulses	Well tolerated, but may cause rash or skin irritation No safety concerns
Anticonvulsants **Carbamazepine** **Gabapentin** **Lamotrigine** **Phenytoin** **Pregabalin**	Work centrally. **Gabapentin** and **pregabalin** have specific GABA binding sites; also produce calcium channel blockade. **Carbamazepine** may limit influx of sodium ions across cell membranes, depressing synaptic transmission or decreasing summation of temporal stimulation. **Lamotrigine** and **phenytoin** produce sodium channel blockade. **Lamotrigine** inhibits release of glutamate	Side effects: Drowsiness, dizziness, GI upset, ataxia, nystagmus at high doses Safety concerns: **Gabapentin:** Concerns only in patients treated for epilepsy **Carbamazepine:** Bone marrow suppression/blood dyscrasias, hypersensitivity/anaphylaxis, hepatic dysfunction, SIADH **Lamotrigine:** Stevens-Johnson syndrome
Antidepressants, Serotonin-norepinephrine Reuptake Inhibitors (SNRIs) **Duloxetine** **Venlafaxine**	Centrally inhibit serotonin-norepinephrine reuptake inhibition. Possible calcium channel blockade	Side effects: Drowsiness, dizziness, GI upset, activation or agitation Safety concerns: Syndrome of inappropriate antidiuretic hormone secretion (SIADH), suicidal ideation
Antidepressants, Tricyclic **Amitriptyline** **Amoxapine** **Desipramine** **Doxepin** **Nortriptyline** **Protriptyline**	Work centrally and possibly peripherally. Sodium channel blockade. Inhibition of norepinephrine and serotonin reuptake. Possible calcium channel blockade and central and peripheral alpha-adrenergic effects	Side effects: Drowsiness, dizziness, forgetfulness, constipation, blurred vision, dry mouth, weight gain, sexual dysfunction Safety concerns: Cardiac conduction changes, orthostatic hypotension, serotonin syndrome (with other serotonergic agents)
Counterirritants, Topicals, **Capsaicin**	Vanilloid receptor antagonist suppresses spinal cord pain signaling; depletes the neuron of substance P and prevents reaccumulation	Side effects: Burning sensation at site of application Safety concerns: Few, but may cause burning of mucous membranes if applied inadvertently
COX-2 Inhibitors[*] **Celecoxib** **Rofecoxib**[†] **Valdecoxib**[‡]	Work peripherally by inhibiting COX-2 enzyme, reducing inflammation and pain. Possible central effect on NMDA	Side effects: GI discomfort, drowsiness, increased blood pressure, lower extremity edema Safety concerns: Increased

		cardiovascular events
Muscle Relaxants, Centrally Acting **Baclofen**	Work centrally. GABA-B agonism inhibits pain signaling. Inhibits transmission of reflexes at spinal cord level, possibly by hyperpolarization of primary afferent fiber terminals	Side effects: Drowsiness, dizziness, GI upset, ataxia, cognitive impairment Safety concerns: Respiratory depression with unintentional overdose
N-methyl-d-aspartate (NMDA) Inhibitors **Ketamine**	Direct action on the cortex and limbic system of CNS by NMDA inhibition	Side effects: Drowsiness, dizziness, dysphoria, dissociation, hallucinations Safety concerns: Hypersensitivity
NSAIDs* **Diclofenac** **Ibuprofen** **Naproxen** **Salsalate**	Work peripherally on inflammation and pain by inhibition of COX-1/COX-2 enzymes. Some central effects on AMPA and/or NMDA	Side effects: Gastrointestinal discomfort (nausea, cramping, dyspepsia), drowsiness, increased blood pressure, bruising/petechiae, lower extremity edema Safety concerns: Gastrointestinal ulceration, bleeding/impaired coagulation, renal impairment
Opioids, Opioid-like Agents **Tramadol**	Work centrally by weak mu opioid receptor agonism and serotonin-norepinephrine reuptake inhibition. Possible sodium, calcium, and/or potassium channel blockade	Side effects: Drowsiness, dizziness, gastrointestinal upset, agitation Safety concerns: Seizures (usually with overdosage), serotonin syndrome with antidepressants
Opioids, Oral **Hydromorphone**† **Morphine** **Oxycodone**	Central: Binds to opioid receptors in CNS to inhibit ascending transmission of nociceptive signals; activates midbrain descending pain controls. Peripheral: Binds to opioid receptors on peripheral nerves, decreasing pain signaling	Side effects: Sedation, drowsiness, dizziness, nausea, constipation, itching/hives, urinary hesitancy, sexual dysfunction due to decreased sex hormone levels Safety concerns: Respiratory depression (rare in ambulatory settings), immune dysfunction via lymphocyte depletion
Opioids, Transdermal **Fentanyl** **Transdermal System**§	As for oral opioids	As for oral opioids

*FDA requested labeling for COX-2 agents to include boxed warning highlighting potential increased risk of cardiovascular (CV) events; FDA requested revised labeling for NSAIDs to provide more specific information about potential CV and GI risks.
†Removed from market in 2005 at FDA request because of safety issues.
‡Removed from market in 2004 at FDA request because of safety issues.
§Public health advisory issued July 2005 by FDA regarding the safe use of transdermal fentanyl patches for pain control.