

ACETAMINOPHEN

(Paracetamol)

THERAPEUTICS

Brands

- Tempra, Mapap, Acephen, Oral: Tylenol, Intravenous: Ofirmev

Generic?

Yes



Class

- Nonopioid analgesic

Commonly Prescribed For

(FDA approved in bold)

- **Pain**
- **Fever**
- Osteoarthritis
- Headaches, arthritis, painful inflammatory disorders
- Musculoskeletal pain
- Acute migraine headaches
- Postoperative pain
- Perineal pain in the early postpartum period



How the Drug Works

- Although not fully elucidated, mechanisms which may significantly contribute to acetaminophen-induced analgesia potentially include: inhibiting the synthesis of prostaglandins in the central nervous system, and affecting nitric oxide, serotonergic opiodergic, and/or cannabinoid signaling pathways

How Long until It Works

- Oral: with 1 hour
- IV: within about 5–10 minutes

If It Works

- Continue to use

If It Doesn't Work

- Some patients only have a partial response and in others, discomfort may persist or continue to wax and wane without stabilization of pain
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose (to a maximum oral dose of 1 g), switching to another agent or route, adding an appropriate augmenting agent, or utilizing an entirely different nonpharmacologic approach (e.g. neuromodulation)

- Consider biofeedback or hypnosis for pain
- Consider physical medicine approaches to pain relief
- Consider the presence of noncompliance and counsel patient
- Switch to another agent with fewer side effects
- Consider evaluation for another diagnosis or for a comorbid condition (e.g. medical illness, substance abuse, etc.)



Best Augmenting Combos for Partial Response or Treatment Resistance

- Consider adding an opioid or other agent with analgesic properties

Tests

- None for healthy individuals
- Consider checking liver function tests for long-term use

ADVERSE EFFECTS (AEs)

How Drug Causes AEs

- Uncertain; however, AE mechanisms likely overlap somewhat with mechanisms of action
- Large doses of acetaminophen may yield significant amounts of the hepatotoxic metabolite, N-acetyl-*p*-benzoquinone imine (NAPQI)

Notable AEs

- Elevation in hepatic transaminases (usually borderline)
- Hypotension
- Headache
- Rash
- Abdominal pain, nausea, vomiting
- Anemia
- Hepatitis, liver function abnormalities
- Insomnia
- Fatigue
- Bronchospasm
- Infusion site pain with IV formulation



Life-Threatening or Dangerous AEs

- Severe potentially fatal hepatotoxicity
- Renal insufficiency
- Hypersensitivity reactions, anaphylactoid reaction/anaphylactic shock

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Howard S. Smith and Marco Pappagallo

Excerpt

[More information](#)**ACETAMINOPHEN** (continued)**Weight Gain**

- Unusual

**Sedation**

- Unusual

**What to Do about AEs**

- Reduce dose
- Administer tablet with food or milk in attempts to decrease rate of absorption

Best Augmenting Agents for AEs

- Many side effects cannot be improved with an augmenting agent

- Consider multiple doses of activated charcoal or hemodialysis for severe cases

Long-Term Use

- Safe for long-term use. (Although “safe” long-term maximal dose is somewhat controversial ≤ 3 g/day is probably better than 4 g/day with respect to the development of hepatic insult with long-term therapy)

Habit Forming

- No

How to Stop

- No need to taper

Pharmacokinetics

- Half-life elimination (prolonged following toxic doses):
 - Adults: ~ 2 hours (range: 2–3 hours); may be slightly prolonged in severe renal insufficiency (creatinine clearance < 30 mL/minute): 2.5–3 hours
- Time to peak concentration serum: Oral: immediate release: 10–60 minutes (may be delayed in acute overdoses); IV: 15 minutes
- Excretion: Urine ($> 5\%$ unchanged; 60% to 80% as glucuronide metabolites; 20% to 30% as sulfate metabolites; $\sim 8\%$ cysteine and mercapturic acid metabolites)
- Metabolism
 - At normal therapeutic dosages, primarily hepatic metabolism to sulfate and glucuronide conjugates, while a small amount is metabolized by CYP2E1 to a highly reactive intermediate, *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is conjugated rapidly with glutathione and inactivated to nontoxic cysteine and mercapturic acid conjugates (CYP3A4 and CYP1A2 provide additional minor pathways)
 - At toxic doses, even as little as 4 g daily in certain circumstances (e.g. especially states of glutathione storage depletion such as pre-existing hepatic injury, prolonged fasting/malnutrition, chronic alcohol abusers/consumption of more than three alcoholic drinks per day, certain patients with myopathies). (Cases of hepatotoxicity at daily acetaminophen dosages < 4 g/day have been reported): glutathione conjugation becomes insufficient to meet the metabolic demand causing an increase in NAPQI concentrations, which may cause hepatic cell necrosis. Two other minor metabolic pathways are: hydroxylation to form

DOSING AND USE**Usual Dose Range**

- 1–4 g/day

Dosage Forms

- Oral: Tablets: 325 mg, 500 mg
- Oral: Tylenol arthritis, extended relief tablets: 650 mg caplet
- IV: 1 g

How to Dose

- Pain management: 325–1000 mg every 4–6 hours; maximum daily dose 4 g/day

**Dosing Tips**

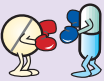
- Taking with food may decrease the rate of absorption

Overdose

- Acute overdose may cause severe hepatotoxicity, severe acute nephrotoxicity, including: nausea, vomiting, diaphoresis, anorexia, pancytopenia, rhabdomyolysis, hypotension, hyperglycemia, pancreatitis, electrolyte abnormalities (likely due to increased fractional urinary electrolyte excretion), early metabolite acidosis, coma, and death
- Early and appropriate supportive treatment including *N*-acetylcysteine should be instituted

3-hydroxy-acetaminophen and methoxylation to form M3-methoxy-acetaminophen (which may then be conjugated with glucuronide or sulfate). Oral administration is subject to first-pass metabolism.

- Primarily absorbed in small intestine (rate of absorption dependent upon gastric emptying), minimal gastric absorption. Protein binding is 10–25% (8–43% at toxic concentrations)



Drug Interactions

- Acetaminophen (particularly when administered in high doses) may produce a mild elevation of prothrombin time (PT), international normalized ratio (INR) (perhaps via inhibition or reduction of vitamin-K-dependent coagulation factors (especially the reduction functional factor VII))
- Concomitant administration of acetaminophen with diflunisal produces about a 50% increase in plasma levels of acetaminophen in healthy volunteers
- INH may affect the activity of CYP2E1 although this likely has no clinically significant effects on usual doses of acetaminophen
- St. John's wort may decrease acetaminophen levels



**Other Warnings/
Precautions**

- Some products may contain phenylalanine

Do Not Use

- Hypersensitivity or anaphylaxis to any acetaminophen-like or -containing agents
- In conjunction with alcohol
- Over 4 g/day
- In patients with severe liver injury

SPECIAL POPULATIONS

Renal Impairment

- Use with caution in chronic renal insufficiency. Use low dose and monitor frequently

Hepatic Impairment

- Use with caution in patients with significant disease

Cardiac Impairment

- No significant deleterious cardiac effects

Elderly

- May have certain advantages over other analgesic agents if relatively low doses are utilized

Disease-Related Concerns

- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥ 3 alcoholic drinks/day may increase the risk of liver damage
- G6PD deficiency: Use with caution in patients with known G6PD deficiency; rare reports of hemolysis have occurred
- Hepatic impairment: Use with caution in patients with hepatic impairment or active liver disease; use of the IV formulation is contraindicated in patients with severe active liver disease
- Hypovolemia: Use the IV formulation with caution in patients with severe hypovolemia (e.g. due to dehydration or blood loss)
- Renal impairment: Use with caution in patients with severe renal impairment; consider dosing adjustments



Pregnancy

- Category C

Breast-feeding

- Acetaminophen is excreted in breast milk. Use caution

THE ART OF PAIN PHARMACOLOGY

Potential Advantages

- No significant GI mucosal insult or excessive bleeding/GI bleeding
- IV formulation can be used while NPO

Potential Disadvantages

- Avoid in patients with hepatic injury
- Use caution with long-term therapy in patients receiving ≥ 3 g/day

Primary Target Symptoms

- Pain
- Fever



Pearls

- No significant effects on platelet function or GI mucosa

ACETAMINOPHEN (continued)

- Numerous combination products, formulations (e.g. meltaways, liquid), and routes available (e.g. per rectum)
- Although not available in the United States, the time of onset with effervescent acetaminophen, 1000 mg (single dose), is significantly faster than with tablet acetaminophen, 1000 mg. Median time to onset of analgesia is 20 minutes (effervescent) versus 45 minutes (tablet), and median time to meaningful pain relief is 45 minutes (effervescent) versus 60 minutes (tablet). The difference may be due to significantly faster absorption with the effervescent form
- Acetaminophen has been formulated in controlled-release sprinkles, which currently are not available in the United States. The extended-release Tylenol Arthritis Extended Relief caplets are available in the United States. This 650-mg caplet is a unique bilayer; the first layer dissolves quickly (roughly about half the dose), whereas the second layer is time released to provide 8 hours of relief. If an overdose of this caplet is taken, it may be appropriate to repeat an additional plasma acetaminophen level 4 to 6 hours after the initial level
- IV formulation can be utilized in the perioperative period while NPO



Suggested Reading

Chou D, Abalos E, Gyte GM, Gülmezoglu AM. Paracetamol/acetaminophen (single administration) for perineal pain in the early postpartum period. *Cochrane Database Syst Rev* 2010 Mar 17;**(3)**:CD008407.

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Macario A, Royal MA. A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. *Pain Pract* 2011;**11**(3):290–6.

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Smith HS. Perioperative intravenous acetaminophen and NSAIDs. *Pain Med* 2011;**12**(6):961–81.

Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database Syst Rev* 2008 Oct 8;**(4)**:CD004602.

ALMOTRIPTAN

THERAPEUTICS

Brands

- Axert, Almogram

Generic?

No



Class

- Triptan

Commonly Prescribed For

(FDA approved in bold)

- Migraine



How the Drug Works

- Selective 5-HT₁ receptor agonist, working predominantly at the B, D, and F receptor subtypes. Effectiveness may be due to blocking the transmission of pain signals from the trigeminal nerve to the trigeminal nucleus caudalis and preventing release of inflammatory neuropeptides rather than just causing vasoconstriction

How Long until It Works

- 1 hour or less

If It Works

- Continue to take as needed. Patients taking acute treatment more than 2 days/week are at risk for medication overuse headache, especially if they have migraine

If It Doesn't Work

- Treat early in the attack: triptans are less likely to work after the development of cutaneous allodynia, a marker of central sensitization
- For patients with partial response or reoccurrence, add an NSAID
- Change to another agent



Best Augmenting Combos for Partial Response or Treatment Resistance

- NSAIDs or neuroleptics are often used to augment response

Tests

- None required

ADVERSE EFFECTS (AEs)

How Drug Causes AEs

- Direct effect on serotonin receptors

Notable AEs

- Tingling, flushing, sensation of burning, vertigo, sensation of pressure, heaviness, nausea



Life-Threatening or Dangerous AEs

- Rare cardiac events including acute MI, cardiac arrhythmia, and coronary artery vasospasm have been reported

Weight Gain

- Unusual



Sedation

- Unusual



What to Do about AEs

- In most cases, only reassurance is needed. Lower dose, change to another triptan, or use an alternative headache treatment

Best Augmenting Agents for AEs

- Treatment of nausea with antiemetics is acceptable. Other AEs improve with time

DOSING AND USE

Usual Dosage Range

- 6.25–12.5 mg

Dosage Forms

- Tablets: 6.25 and 12.5 mg

How to Dose

- Tablets: Most patients respond best at 12.5 mg oral dose. Give 1 pill at the onset of an attack and repeat in 2 hours for a partial response or if headache returns. Maximum 25 mg/day. Limit 10 days per month



Dosing Tips

- Treat early in attack

ALMOTRIPTAN (continued)**Overdose**

- May cause hypertension, cardiovascular symptoms. Other possible symptoms include seizure, tremor, extremity erythema, cyanosis or ataxia. For patients with angina, perform ECG and monitor for ischemia for at least 20 hours

Long-Term Use

- Monitor for cardiac risk factors with continued use

Habit Forming

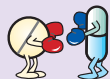
- No

How to Stop

- No need to taper. Patients who overuse triptans often experience withdrawal headaches lasting up to several days

Pharmacokinetics

- Half-life about 3 hours. T_{max} 2.5 hours. Bioavailability is 80%. Metabolized by MAO-A enzyme as well as cytochrome P450 (CYP3A4 and CYP2D6) isozymes. 35% protein binding

**Drug Interactions**

- MAO inhibitors may make it difficult for drug to be metabolized
- Theoretical interactions with SSRI/SNRI. It is unclear whether triptans pose any risk for the development of serotonin syndrome in clinical practice
- Minimal increase in concentration with CYP3A4 inhibitors - no need for dose adjustment

Do Not Use

- Within 2 weeks of MAO inhibitors, or 24 hours of ergot-containing medications such as dihydroergotamine
- Patients with proven hypersensitivity to eletriptan, known cardiovascular disease, uncontrolled hypertension, or Prinzmetal's angina
- Almotriptan was not studied in patients with hemiplegic and basilar migraine
- May worsen symptoms in ischemic bowel disease

SPECIAL POPULATIONS**Renal Impairment**

- Concentration increases in those with moderate-severe renal impairment (creatinine clearance less than 30 mL/minute). May be at increased cardiovascular risk

Hepatic Impairment

- Drug metabolism may be decreased. Do not use with severe hepatic impairment

Cardiac Impairment

- Do not use in patients with known cardiovascular or peripheral vascular disease

Elderly

- May be at increased cardiovascular risk

**Children and Adolescents**

- Safety and efficacy have not been established
- Triptan trials in children were negative, due to higher placebo response

**Pregnancy**

- Category C: Use only if potential benefit outweighs risk to the fetus. Migraine often improves in pregnancy, and other acute agents (opioids, neuroleptics, prednisone) have more proven safety

Breast-Feeding

- Almotriptan is found in breast milk. Use with caution

THE ART OF PAIN PHARMACOLOGY**Potential Advantages**

- Effective with good consistency and excellent tolerability, even compared to other oral triptans. Less risk of abuse than opioids or barbiturate-containing treatments

Potential Disadvantages

- Cost, and the potential for medication overuse headache. May not be as effective as other triptans

Primary Target Symptoms

- Headache pain, nausea, photo- and phonophobia

**Pearls**

- Early treatment of migraine is most effective
- Lower AEs compared to other triptans. Good consistency and pain-free response, making it a good choice for patients with anxiety who are prone to medication side effects

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Excerpt

[More information](#)(continued) **ALMOTRIPTAN**

- May not be effective when taken during the aura, or before headache begins
- In patients with “status migrainosus” (migraine lasting more than 72 hours) neuroleptics and dihydroergotamine are more effective
- Triptans were not originally studied for use in the treatment of basilar or hemiplegic migraine
- Patients taking triptans more than 10 days/month are at increased risk of medication overuse headache which is less responsive to treatment
- Chest and throat tightness are usually benign and may be related to esophageal spasm rather than cardiac ischemia. These symptoms occur more commonly in patients without cardiac risk factors



Suggested Reading

Diener HC, Gendolla A, Gebert I, Beneke M. Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial. *Eur Neurol* 2005;**53**(Suppl 1):41–8.

Dodick D, Lipton RB, Martin V, *et al.* Triptan Cardiovascular Safety Expert Panel. Consensus statement: cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. *Headache* 2004;**44**(5):414–25.

Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT (1B/1D)

agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; **358**(9294):1668–75.

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[More information](#)

AMITRIPTYLINE

THERAPEUTICS

Brands

- Elavil, Triptafen, Tryptanol, Endep, Elatrol, Tryptizol, Triptiline, Laroxyl, Saroten, Triptyl, Redomex

Generic?

Yes



Class

- Tricyclic antidepressant (TCA)

Commonly Prescribed For

(FDA approved in bold)

- **Depression**
- Migraine prophylaxis
- Tension-type headache prophylaxis
- Diabetic neuropathy
- Post-herpetic neuralgia
- Peripheral neuropathy with pain
- Back or neck pain
- Phantom limb pain
- Fibromyalgia
- Bulimia nervosa
- Insomnia
- Anxiety
- Nocturnal enuresis
- Pseudobulbar affect
- Arthritic pain



How the Drug Works

- Blocks serotonin and norepinephrine reuptake pumps increasing their levels within hours with analgesic effects generally by 1 week, but antidepressant effects can take several weeks. Effect is more likely related to adaptive changes in serotonin and norepinephrine receptor systems over time. It also has anticholinergic and antihistamine properties which most likely contribute to the sedation in treating insomnia
- Amitriptyline may provide analgesia via other mechanisms including acting as a local anesthetic (blocking sodium channels)

How Long until It Works

- Migraines: effective in as little as 2 weeks, but can take up to 3 months on a stable dose to see full effect

- Neuropathic pain: usually some effect within 4 weeks
- Insomnia, anxiety, depression: may be effective immediately, but effects often delayed 2 to 4 weeks

If It Works

- Migraine: goal is a 50% or greater reduction in migraine frequency or severity. Consider tapering or stopping if headaches remit for more than 6 months or if considering pregnancy
- Neuropathic pain: the goal is to reduce pain intensity and symptoms, but usually does not produce remission
- Insomnia: continue to use if tolerated and encourage good sleep hygiene

If It Doesn't Work

- Increase to highest tolerated dose
- Migraine: address other issues, such as medication overuse, other coexisting medical disorders, such as anxiety, and consider changing to another agent or adding a second agent
- Chronic pain: either change to another agent or add a second agent
- Insomnia: if no sedation occurs despite adequate dosing, stop and change to another agent



Best Augmenting Combos for Partial Response or Treatment Resistance

- Migraine: for some patients, low-dose polytherapy with 2 or more drugs may be better tolerated and more effective than high-dose monotherapy. May use in combination with AEDs, antihypertensives, natural products, and nonmedication treatments, such as biofeedback, to improve headache control
- Chronic pain: AEDs, such as gabapentin, pregabalin, carbamazepine, or mexiletine, are agents used for neuropathic pain. Opioids are appropriate for long-term use in some cases but require careful monitoring

Tests

- Check ECG for QT corrected (QTc) prolongation at baseline and when increasing dose, especially in those with a personal or family history of QTc prolongation, cardiac arrhythmia, heart failure, or recent MI. If patient is on diuretics, measure potassium and magnesium at baseline and periodically with treatment

ADVERSE EFFECTS (AEs)

How Drug Causes AEs

- Anticholinergic and antihistaminic properties are causes of most common AEs. Blockade of alpha-adrenergic-1 receptor may cause orthostasis and sedation

Notable AEs

- Constipation, dry mouth, blurry vision, increased appetite, nausea, diarrhea, heartburn, weight gain, urinary retention, sexual dysfunction, sweating, itching, rash, fatigue, weakness, sedation, nervousness, restlessness

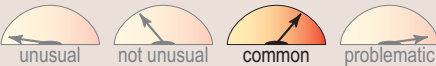


Life-Threatening or Dangerous AEs

- Orthostatic hypotension (may block alpha-adrenergic-1 receptor), tachycardia, QTc prolongation, and rarely death
- Increased intraocular pressure
- Paralytic ileus, hyperthermia
- Rare activation of mania or suicidal ideation
- Rare worsening of existing seizure disorders

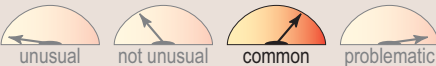
Weight Gain

- Common



Sedation

- Common



What to Do about AEs

- For minor AEs, lower dose or switch to another agent. If tiredness/sedation are bothersome, change to a secondary amine (e.g. nortriptyline). For serious AEs, lower dose and consider stopping

Best Augmenting Agents for AEs

- Try magnesium for constipation. For migraine, consider using with agents that cause weight loss (e.g. topiramate)

Dosage Forms

- Tablets: 10, 25, 50, 75, 100, and 150 mg

How to Dose

- Initial dose 10–25 mg/day taken about 1 hour before retiring. Effective range from 10 to 400 mg but typically 150 mg or less



Dosing Tips

- Start at a low dose, usually 10 mg, and titrate up every few days as tolerated. Low doses are often effective for pain even though they are below the usual effective antidepressant dose.

Overdose

- Cardiac arrhythmias and ECG changes; death can occur. CNS depression, convulsion, severe hypotension, and coma are not rare. Patients should be hospitalized. Sodium bicarbonate can treat arrhythmias and hypotension. Treat shock with vasopressors, oxygen, or corticosteroids

Long-Term Use

- Safe for long-term use

Habit Forming

- No

How to Stop

- Taper slowly to avoid withdrawal, including rebound insomnia. Withdrawal usually lasts less than 2 weeks. For patients with well-controlled pain disorders, taper very slowly (over months) and monitor for recurrence of symptoms

Pharmacokinetics

- Metabolized by CYP450 system, especially CYP2D6, 1A2. Half-life 10–28 hours and metabolized to nortriptyline



Drug Interactions

- CYP2D6 inhibitors (duloxetine, paroxetine, fluoxetine, bupropion), cimetidine, and valproic acid can increase drug concentration
- Fluvoxamine, a CYP1A2 inhibitor, prevents metabolism to nortriptyline and increased amitriptyline concentrations
- Tramadol increases risk of seizures in patients taking TCAs
- Phenothiazines may increase tricyclic levels
- Enzyme inducers, such as rifamycin, smoking, phenobarbital can lower levels

DOSING AND USE

Usual Dose Range

- Migraine, pain: 10–100 mg/day
- Depression, anxiety: 50–150 mg/day

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[More information](#)**AMITRIPTYLINE** (continued)

- Use with clonidine has been associated with increases in blood pressure and hypertensive crisis (however, this is not common)
- May reduce absorption and bioavailability of levodopa
- May alter effects of antihypertensive medications and prolongation of QTc, especially problematic in patients taking drugs that induce bradycardia
- Use together with anticholinergics can increase AEs (i.e. risk of ileus)
- Methylphenidate may inhibit metabolism and increase AEs
- Use within 2 weeks of MAO inhibitors may risk serotonin syndrome

**Other Warnings/
Precautions**

- May increase risk of seizure

Do Not Use

- Proven hypersensitivity to drug or other TCAs
- In acute recovery after MI or uncompensated heart failure
- In conjunction with antiarrhythmics that prolong QTc interval
- In conjunction with medications that inhibit CYP2D6

SPECIAL POPULATIONS**Renal Impairment**

- Use with caution, may need to lower dose

Hepatic Impairment

- Use with caution, may need to lower dose

Cardiac Impairment

- Do not use in patients with recent MI, severe heart failure, history of QTc prolongation, or orthostatic hypotension

Elderly

- More sensitive to AEs, such as sedation, hypotension. Start with lower doses
- Listed in "Beers Criteria". Thus, if going to use at all in patients over age 65, use with extreme caution

**Children and Adolescents**

- Some data for children over 12 and an appropriate treatment for adolescents with migraine, especially children with insomnia who are not overweight. In children younger than 12, most commonly used at low doses for treatment of enuresis

**Pregnancy**

- Category C: Crosses the placenta and may cause fetal malformations or withdrawal. Generally not recommended for the treatment of pain or insomnia during pregnancy. For patients with depression or anxiety, SSRIs may be safer than TCAs

Breast-Feeding

- Some drug is found in breast milk and use while breast-feeding is not recommended.

THE ART OF PAIN PHARMACOLOGY**Potential Advantages**

- Proven effectiveness in multiple pain disorders. May be beneficial for insomnia and depression, which are common in patients with chronic pain

Potential Disadvantages

- AEs are often greater than with SSRIs or SNRIs and many AEDs. More anticholinergic AEs than other TCAs. Weight gain and sedation can be problematic

Primary Target Symptoms

- Headache frequency and severity
- Reduction in neuropathic pain

**Pearls**

- In patients with chronic pain, offers relief at doses below usual antidepressant doses, and can treat coexisting insomnia
- For patients with significant anxiety or depressive disorders, not as effective as newer drugs with more AEs. Consider treatment of depression or anxiety with another agent together with a low dose of amitriptyline or other TCA for pain
- TCAs can often precipitate mania in patients with bipolar disorder. Use with caution
- Despite interactions, expert psychiatrists may use with MAO inhibitors for refractory depression
- Many patients do not improve. The NNT for moderate pain relief in neuropathic pain is 2–3
- Increases non-REM sleep time and decreases sleep latency
- TCAs may increase risk of metabolic syndrome