

These are the most common OTC drug interactions by severity. When in doubt — talk to your pharmacist.

X AVOID — Do Not Combine	
COMBINATION	WHY IT MATTERS
Ibuprofen + Aspirin	Both are NSAIDs — combining doubles GI bleeding risk and blocks aspirin's cardioprotective effect. Take aspirin 30 min before ibuprofen if both needed.
Ibuprofen + Naproxen	Two NSAIDs at once. No added pain relief — only increased risk of GI ulcers, kidney damage, and cardiovascular events.
Acetaminophen + NyQuil	NyQuil already contains acetaminophen. Adding extra Tylenol can exceed the 4,000 mg/day limit, risking liver damage. Check all 'multi-symptom' labels.
Diphenhydramine + Alcohol	Benadryl + alcohol = extreme sedation, impaired coordination, and respiratory depression. Even one drink amplifies the effect significantly.
Diphenhydramine + Sleep Aids	ZzzQuil, Unisom, and many PM formulas already contain diphenhydramine. Stacking causes severe over-sedation and anticholinergic toxicity.
Antacids + Certain Antibiotics	Calcium/magnesium antacids (Tums, Mylanta) bind to fluoroquinolone and tetracycline antibiotics, reducing absorption by up to 90%. Space them 2+ hours apart.
! USE CAUTION — Monitor Closely	
COMBINATION	WHY IT MATTERS
Ibuprofen + Blood Pressure Meds	NSAIDs can blunt the effect of ACE inhibitors and diuretics, raising blood pressure. If you're on BP meds, try acetaminophen instead.
Melatonin + Sedatives / Sleep Aids	Melatonin stacks with any CNS depressant (diphenhydramine, alcohol, benzos). Increases drowsiness and next-day grogginess. Start with the lowest effective dose (0.5–1 mg).
Aspirin + Fish Oil (high dose)	Both thin the blood. At high fish oil doses (3+ g/day) combined with aspirin, bruising and bleeding time increase. Fine at standard supplement doses.
Decongestants + Stimulants / Caffeine	Pseudoephedrine (Sudafed) + high caffeine or stimulant weight-loss supplements can spike heart rate and blood pressure. Avoid in people with heart conditions.
Iron Supplements + Antacids	Antacids reduce stomach acid needed to absorb iron. Separate by at least 2 hours. Take iron on an empty stomach with vitamin C for best absorption.
St. John's Wort + Any Medication	This herbal supplement induces liver enzymes that break down many drugs faster — reducing their effectiveness. Affects hormonal contraceptives, blood thinners, and more.
~ TIMING MATTERS — Space These Out	
COMBINATION	WHY IT MATTERS
Antacids + Any OTC Drug	Antacids alter stomach pH and can affect absorption of many drugs. General rule: take other medications 1–2 hours before or after antacids.
Calcium Supplements + Iron	Calcium blocks iron absorption. Take them at separate meals — morning iron, evening calcium works well for most people.
Zinc + Copper Supplements	Long-term high-dose zinc (50+ mg/day) depletes copper. If taking therapeutic zinc, add a small copper supplement or choose a zinc-copper combo product.

5 Rules to Live By

1. Always read the 'Active Ingredients' label — 'multi-symptom' products often stack acetaminophen, antihistamines, and decongestants.
2. One NSAID at a time. Never combine ibuprofen, naproxen, or aspirin.
3. Check PM formulas. Any product with 'PM', 'Night', or 'Sleep' likely contains diphenhydramine — do not add more.
4. Supplements count. Fish oil, St. John's Wort, and high-dose vitamins interact with OTC and Rx drugs alike.
5. Talk to your pharmacist before combining anything you're unsure about — it's free and takes 2 minutes.

! ACETAMINOPHEN — The Hidden Danger

Safe daily limit	4,000 mg/day for healthy adults. Many providers recommend staying under 3,000 mg/day to be safe.
Standard Tylenol tablet	325–500 mg per tablet. Extra Strength = 500 mg. Take up to 2 tabs every 6 hours.
NyQuil / DayQuil	325–650 mg acetaminophen per dose. Adding Tylenol on top can easily exceed the daily limit.
Excedrin Migraine	250 mg acetaminophen + 250 mg aspirin + 65 mg caffeine per tablet. Not a 'plain' pain reliever.
Percocet / Vicodin (Rx)	Contain 325 mg acetaminophen each. Critical to track if taking OTC acetaminophen simultaneously.
Alcohol + Acetaminophen	Regular alcohol use + acetaminophen = serious liver damage risk. Even moderate drinking lowers the safe threshold.

* WATCH FOR STACKING — Products That Overlap

DayQuil + Tylenol	Both contain acetaminophen. A very common ER visit cause.
ZzzQuil + Benadryl	Both are diphenhydramine — you're doubling the dose.
Excedrin + Ibuprofen	Excedrin contains aspirin — two NSAIDs at once.
Robitussin DM + NyQuil	Both may contain dextromethorphan — overdose risk.
Mucinex D + Sudafed	Both contain pseudoephedrine — dangerous heart/BP spike.
Zyrtec + Benadryl	Two antihistamines — extreme sedation, dry mouth, confusion.

Sources

1. FDA Drug Interactions: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-drug-and-drug-dietary-supplement-interactions>
2. NIH MedlinePlus — Drug Interactions: <https://medlineplus.gov/druginteractions.html>
3. Drugs.com Interaction Checker: https://www.drugs.com/drug_interactions.html
4. Cleveland Clinic — Acetaminophen Safety: <https://my.clevelandclinic.org/health/drugs/18024-acetaminophen>
5. ASHP Drug Information (accessed July 2026): <https://www.ashp.org/pharmacy-practice/policy-positions-and-guidelines>

This cheat sheet is for educational purposes only and does not constitute medical advice. Drug interactions depend on individual health conditions, doses, and other medications. Always talk to your pharmacist or healthcare provider before making medication decisions.

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