SUBSTANCE USE DISORDER AGENT

Disulfiram

Antabuse (brand discontinued in the US; generics available)

Aldehyde dehydrogenase inhibitor used as an aversive deterrent in motivated, supervised patients seeking enforced abstinence from alcohol.

USUAL ADULT DOSE	DURATION OF EFFECT	METABOLISM	ONSET
250 mg/day PO (125-500 mg)	Up to 14 days after last dose	Hepatic; inhibits CYP2E1, CYP1A2	Full ALDH blockade by 12 h

⚠ FDA BOXED WARNING

Disulfiram must never be given to a patient who is in a state of alcohol intoxication, or without the patient's full knowledge; the physician should instruct relatives accordingly.

INDICATIONS

- FDA-approved as an aversive adjunct in carefully selected, cooperative adults with alcohol use disorder who want enforced sobriety plus psychosocial treatment.
- Third-line after naltrexone and acamprosate in the APA 2018 and VA/DoD 2021 guidelines, reserved for patients committed to total abstinence.
- Blinded trials show no advantage over placebo; open supervised administration by a partner, clinic or pharmacy is what produces benefit.
- Has no role in managing alcohol withdrawal and does nothing for craving; it deters drinking only through anticipated punishment.
- Studied off-label for cocaine use disorder through dopamine beta-hydroxylase inhibition, with mixed and largely disappointing results.
- Requires informed consent and a patient who understands the reaction; covert administration is prohibited by the boxed warning.

DOSING & TITRATION

- Never give the first dose until at least **12 h** after the last drink and the patient is fully sober; a zero breath alcohol reading is ideal.
- Start **500 mg** once daily for one to two weeks, then maintain on **250 mg** daily; the usual range is 125-500 mg and the max is **500 mg/day**.
- Dose at bedtime if sedation is a problem, or in the morning if it disturbs sleep; a single daily dose is all that is needed.
- Arrange observed dosing by a spouse, family member, pharmacy or clinic, since supervision is the single strongest predictor of benefit.
- Counsel about hidden alcohol in mouthwash, cough and cold syrups, hand sanitizer, aftershave, vinegars, sauces, desserts and some topical preparations.
- Treatment typically continues one to two years; no taper is required, but warn that drinking can trigger a reaction for two weeks after stopping.

MECHANISM OF ACTION

- Irreversibly inhibits aldehyde dehydrogenase, so acetaldehyde from ethanol accumulates to five to ten times normal and produces the aversive reaction.
- The reaction brings flushing, throbbing headache, nausea, vomiting, tachycardia, hypotension, dyspnea and chest pain within minutes of drinking.
- Because inhibition is irreversible, effect persists until new enzyme is synthesized, which takes up to **14 days** after the last dose.
- Also inhibits dopamine beta-hydroxylase, raising dopamine and lowering norepinephrine, which explains the psychosis risk and the cocaine trials.
- Provides no craving reduction and no reward blockade, so it works only while the patient keeps taking it under observation.

PHARMACOKINETICS

- About **80-95%** of an oral dose is absorbed and rapidly reduced to diethyldithiocarbamate and further to active and inactive metabolites.
- Highly lipophilic with accumulation in fat, so roughly a fifth of a dose remains in the body one to two weeks after stopping.
- Inhibits CYP2E1 and CYP1A2 and impairs oxidative metabolism broadly, raising concentrations of warfarin, phenytoin and oxidized benzodiazepines.
- Full enzyme inhibition takes about **12 h** to develop, which is why the first dose is delayed until the patient is alcohol-free.
- Metabolites are excreted in urine and some carbon disulfide is exhaled, giving the characteristic garlic-like or metallic aftertaste.

ADVERSE EFFECTS

- Drowsiness, fatigue, headache, a metallic or garlic-like aftertaste, acneiform rash and impotence are common in the first weeks of treatment.
- Hepatotoxicity ranging from transaminase elevation to fulminant hepatic failure can appear at any time, including after months of stable therapy.
- Peripheral neuropathy and optic neuritis occur with prolonged use and are the usual reasons to stop after the first year of treatment.
- Psychosis, confusion, delirium and catatonia are dose-related, more likely above **500 mg/day** and in patients with a psychotic disorder.
- The disulfiram-alcohol reaction itself can be fatal, causing arrhythmia, myocardial infarction, respiratory depression, seizure and cardiovascular collapse.
- Hypersensitivity dermatitis is more frequent in people previously sensitized to thiuram derivatives, such as rubber industry workers.

MONITORING

- Baseline liver function tests, then repeat at **2 weeks**, monthly for the first 3 months, and every 3 to 6 months thereafter.
- Baseline complete blood count, basic chemistry and thyroid status; consider an ECG in anyone with cardiac history or risk factors.
- Ask at every visit about numbness, tingling, gait change and visual blurring to catch neuropathy or optic neuritis early.
- Screen for confusion, paranoia or hallucinations, particularly after any dose increase above **250 mg** daily.
- Reconfirm consent, motivation and the supervision arrangement at each visit, since unobserved dosing predicts loss of benefit.

INTERACTIONS & CAUTIONS

- Alcohol in any form is contraindicated, including intravenous drug diluents, elixirs, topical preparations and alcohol-containing food products.
- Metronidazole is contraindicated because the combination can precipitate confusion, psychosis and a severe acute organic brain syndrome.
- Inhibits warfarin metabolism and raises the INR, so anticoagulated patients need INR checks after starting and after any dose change.
- Substantially raises phenytoin concentrations, and increases levels of oxidized benzodiazepines such as diazepam and chlordiazepoxide.
- Contraindicated in severe myocardial disease, coronary occlusion and psychosis; combine cautiously with isoniazid, which can add ataxia and confusion.

SPECIAL POPULATIONS

- Pregnancy: avoid, as human data are limited, case reports describe limb anomalies, and a reaction would expose the fetus to acetaldehyde.
- Lactation: excretion into human milk is unknown and no safety data exist, so alternative pharmacotherapy is preferred while breastfeeding.
- Pediatric safety and effectiveness have not been established and there is no recommended dose for patients under 18 years.
- Geriatric patients are more vulnerable to confusion, neuropathy and cardiovascular consequences of a reaction, so use with particular caution.
- Hepatic: avoid in significant liver disease or cirrhosis; also use caution in diabetes, hypothyroidism, seizure disorder and renal impairment.

PRESCRIBING PEARLS

- It only works observed; unsupervised disulfiram performs no better than placebo in blinded trials.
- Wait **12 h** after the last drink to start, and warn that a reaction is possible 14 days after stopping.
- Check LFTs at baseline and **2 weeks**; hepatitis can appear even after months of stable dosing.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.