SUBSTANCE USE DISORDER AGENT

Varenicline

Chantix, Tyrvaya (nasal spray for dry eye)

Alpha4beta2 nicotinic partial agonist and the single most effective monotherapy for smoking cessation in adults.

USUAL ADULT DOSE	HALF-LIFE	METABOLISM	ONSET
1 mg PO BID after titration	About 24 h	Minimal; 92% renal unchanged	Quit date on day 8 of therapy

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved as an aid to smoking cessation treatment in adults, used together with behavioral support and a defined quit plan.
- Outperformed bupropion, nicotine patch and placebo for abstinence in the EAGLES trial, making it the preferred first-line agent.
- Combining varenicline with a nicotine patch raises abstinence rates further, an off-label strategy supported by randomized evidence.
- Off-label for smokeless tobacco cessation and for e-cigarette cessation, where a 2024 randomized trial showed benefit in young adults.
- Effective and neuropsychiatrically safe in people with stable psychiatric disorders, a group with high smoking-related mortality.
- The nasal spray marketed as Tyrvaya is the same molecule approved for dry eye disease and has no role in tobacco cessation.

DOSING & TITRATION

- Standard titration is **0.5 mg** once daily on days 1-3, **0.5 mg** twice daily on days 4-7, then **1 mg** twice daily from day 8 for 12 weeks.
- Set the quit date for day 8, or use a flexible approach with quitting any time between weeks 2 and 5, or gradual reduction over 12 weeks.
- Successful quitters may continue an additional 12 weeks, for 24 weeks total, which measurably reduces late relapse.
- Take after eating with a full glass of water to limit nausea; if nausea persists, drop back to **0.5 mg** twice daily rather than stopping.
- Creatinine clearance under 30 mL/min: maximum **0.5 mg** twice daily; on hemodialysis the maximum is **0.5 mg** once daily.
- No taper is needed at the end of treatment, though some patients report transient irritability when it is stopped abruptly.

MECHANISM OF ACTION

- Partial agonist at the alpha4beta2 nicotinic acetylcholine receptor, the subtype that mediates nicotine reinforcement and withdrawal.
- Partial stimulation releases about half as much accumbens dopamine as nicotine, which relieves craving and withdrawal symptoms.
- Simultaneous receptor occupancy blocks nicotine binding, so cigarettes smoked during treatment deliver much less reward.
- Acts as a full agonist at alpha7 and alpha3beta4 nicotinic receptors, which may contribute to the prominent nausea.
- Has no monoamine reuptake activity, unlike bupropion, so it does not treat depression and does not lower seizure threshold much.

PHARMACOKINETICS

- Oral absorption is essentially complete with peak concentrations at 3-4 h, and food has no clinically meaningful effect on exposure.
- Undergoes minimal metabolism: roughly **92%** of a dose is excreted unchanged in urine by filtration and active OCT2 secretion.
- Terminal half-life is about **24 h**, so twice-daily dosing reaches steady state within four days of starting or changing the dose.
- No CYP450 metabolism and low protein binding under **20%** mean essentially no pharmacokinetic interactions with psychotropics.
- Renal function is the sole clinically important determinant of exposure, driving dose reduction below a creatinine clearance of 30 mL/min.

ADVERSE EFFECTS

- Nausea affects roughly **30%** of patients, is dose-related and usually mild to moderate; taking the dose after food reduces it substantially.
- Insomnia in about **18%** and vivid or abnormal dreams in about **13%** are the second-most common complaints and often persist.
- Headache, constipation, flatulence and dysgeusia occur; these rarely require discontinuation but do influence adherence.
- The neuropsychiatric boxed warning was removed in 2016 after the EAGLES trial found no excess of serious events versus placebo.
- Seizures occur rarely, in roughly **0.1%**, usually in the first month; avoid or use cautiously in patients with a seizure disorder.
- Alcohol tolerance may fall, with reports of unusual or aggressive behavior and amnesia; advise reducing intake until tolerance is known.

MONITORING

- Baseline renal function with calculated creatinine clearance, since this is the only routinely required laboratory check.
- Ask about mood, agitation, hostility and suicidal ideation at follow-up despite removal of the boxed warning, particularly in psychiatric patients.
- Review nausea, sleep and dream disturbance at weeks 1 and 2, the period when most patients decide whether to continue.
- Track abstinence, cigarettes per day and craving; exhaled carbon monoxide is a simple objective confirmation when available.
- Recheck doses of clozapine, olanzapine and other CYP1A2 substrates within one to two weeks of the patient stopping smoking.

INTERACTIONS & CAUTIONS

- Essentially no cytochrome P450 interactions, which makes varenicline unusually easy to add to complex psychiatric regimens.
- Stopping smoking removes CYP1A2 induction and can nearly double clozapine, olanzapine, fluvoxamine, duloxetine, theophylline and caffeine levels.
- Cimetidine raises varenicline exposure by about **29%** in severe renal impairment and warrants a dose reduction in that setting.
- Adding a nicotine patch increases nausea, headache, vomiting and dizziness even though the combination improves abstinence.
- Alcohol effects can be exaggerated, and case reports describe blackouts and aggression; counsel patients to limit intake.

SPECIAL POPULATIONS

- Pregnancy: human data are limited, behavioral treatment is first-line, and nicotine replacement is generally preferred if pharmacotherapy is needed.
- Lactation: transfer into human milk has not been quantified; weigh the substantial benefit of quitting against uncertain infant exposure.
- Pediatric use is not FDA-approved under 18, although recent trial data support off-label use for vaping cessation in older adolescents.
- Geriatric patients need no special dose except as dictated by renal function, which commonly declines silently with age.
- Renal impairment drives all dose adjustment; no hepatic adjustment is required because hepatic metabolism is negligible.

PRESCRIBING PEARLS

- The neuropsychiatric boxed warning was removed in 2016; EAGLES found no signal versus placebo.
- Quitting smoking lifts CYP1A2 induction, so clozapine and olanzapine levels can nearly double.
- Nausea is dose-related: take after food, and drop to **0.5 mg BID** rather than abandoning it.

References

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World Health Organization. (2024). *WHO clinical treatment guideline for tobacco cessation in adults*. https://www.who.int/publications

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.