

# Cytisine/Cytisinicline

## Frequently Asked Questions



BEHAVIORAL HEALTH &  
WELLNESS PROGRAM  
Department of Psychiatry



National Behavioral  
Health Network

for Tobacco & Cancer Control

from NATIONAL COUNCIL FOR  
MENTAL WELLBEING

## WHAT IS CYTISINE AND WHERE DOES IT COME FROM?

Cytisine (AKA cytisinicline in clinical trials) is a naturally occurring plant compound found in the seeds of the golden chain or golden rain tree. It has been used to help people quit smoking in Eastern and Central Europe since the 1960s. The medication varenicline (formerly branded as Chantix) was developed using cytisine as the lead chemical structure.

## HOW DOES CYTISINE WORK?

Nicotine addiction happens when nicotine activates specific receptors in the brain, especially the  $\alpha 4\beta 2$  nicotinic receptors. When nicotine binds to these receptors, the brain releases chemical messengers like dopamine, which creates a sense of reward and strengthens the urge to keep using nicotine. Cytisine turns down the volume on nicotine's effect in the brain while a person works on breaking the habit of nicotine use.

Cytisine works in two main ways:

- It partially activates the same receptors as nicotine. This reduces cravings and withdrawal symptoms but produces much less dopamine release than nicotine.
- It blocks nicotine from binding to the receptors. As a result, smoking and vaping while taking cytisine feels less rewarding.

## IS CYTISINE SAFE?

Based on the clinical trial evidence available to date, cytisine has a reassuring safety profile. Key findings from clinical trials found:

- No serious adverse events (e.g., suicidal behavior) were reported across any of the trials (Phase 1 through Phase 3).
- The most common side effect was nausea, which was dose-dependent and generally mild.
- Insomnia and abnormal dreams were reported in fewer than 10% of participants in Phase 3 trials.
- Only about 3% of participants stopped treatment due to side effects.

## HOW EFFECTIVE IS CYTISINE? DOES IT WORK AS WELL AS NICOTINE REPLACEMENT THERAPY AND VARENICLINE?

The short answer: When treatment courses are the same length, cytisine and varenicline have similar efficacy, and cytisine appears to have better efficacy than nicotine replacement therapy (NRT).

<b>Study</b>	<b>Comparison</b>	<b>6-Month Abstinence</b>
Walker et al., 2014	cytisine 25 days vs. NRT 8 weeks	cytisine 22%; NRT 15%
Walker et al., 2021	cytisine 12 weeks vs. varenicline 12 weeks	cytisine 12%; varenicline 8%
Courtney et al., 2021	cytisine 25 days vs. varenicline 12 weeks	cytisine 12%; varenicline 13%
Oreskovic et al., 2023	cytisine 4 weeks vs. varenicline 12 weeks	cytisine 23%; varenicline 33%

## WHO IS A GOOD CANDIDATE FOR CYTISINE?

Cytisine may be a strong option for:

- Any adult motivated to quit smoking or vaping: Clinical trials have shown cytisine is just as effective for people who smoke or as for people who vape.
- Patients with chronic obstructive pulmonary disease (COPD): Clinical trials found cytisine worked just as well in COPD patients as in those without — even though COPD patients had smoked longer.
- Patients who previously tried varenicline and had a difficult experience with side effects.

## ARE THERE PATIENTS FOR WHOM VARENICLINE MIGHT BE A BETTER CHOICE?

Yes. Based on current evidence, varenicline may be preferred in the following situations, based on shared decision-making between patient and provider:

- **Pregnancy:** Pregnant individuals. There is no safety data for cytisine in pregnancy. In available studies, varenicline has not been associated with birth defects. The patient’s OB/GYN or pediatrician should help the patient understand the risks of continued smoking versus potential medication risks.
- **Behavioral health:** Patients with significant psychiatric comorbidities. The EAGLES trial established that varenicline does not increase neuropsychiatric risk — even in patients with serious mental illnesses. No equivalent data exist for cytisine yet. Until Phase 4 analyses are available, varenicline remains the better-supported choice when psychiatric comorbidity is a concern.
- **Cost and access:** When insurance coverage and out-of-pocket cost favor varenicline. As of May 2026, cytisine is not yet available in the U.S., and insurance coverage is not yet established. Providers should discuss access and cost with patients before prescribing. Generic varenicline is broadly covered by insurance and Medicare Part D.

## HOW FREQUENTLY IS CYTISINE TAKEN AND AT WHAT DOSE?

Historically, cytisine has had a 25-day schedule that starts high and tapers rapidly every few days. However, the protocol in the ORCA trials was a 12-week cycle like varenicline. The 12-week cytisinicline protocol (3 mg TID) produced significantly higher abstinence rates than both placebo and the six-week duration in ORCA Phase 3.

## CAN CYTISINE BE USED ALONGSIDE OTHER CESSATION TREATMENTS?

Cytisine has not been studied in combination with other prescription cessation medications or NRT. Some studies and physician groups support combining NRT with varenicline, but research is mixed.

Behavioral support (counseling, quitline referral, text-based programs) is compatible with and complementary to cytisine and is encouraged for all patients.

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