Cytisine/Cytisinicline

Prescriber Quick Reference for Nicotine Cessation

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from NATIONAL COUNCIL FOR MENTAL WELLBEING

WHAT IS CYTISINE?

Cytisine (AKA cytisinicline in clinical trials) is a plant-derived partial agonist at α4β2 nicotinic acetylcholine receptors, the same receptor subtype primarily responsible for nicotine dependence. Cytisine has been used for smoking cessation in Eastern and Central Europe since the 1960s. By partially stimulating α4β2 receptors, it reduces craving and withdrawal while simultaneously blocking nicotine from binding — weakening the reward signal if the patient uses nicotine. The medication varenicline (formerly branded as Chantix) was developed using cytisine as the lead chemical structure. However, cytisine and varenicline have important differences that can inform shared decision-making when selecting a treatment option.

MECHANISM OF ACTION

Nicotine Full Agonist	***Varenicline*** Moderate Partial Agonist	***Cytisine*** Low Partial Agonist
High dopamine release, high addiction risk	Moderate dopamine release, low addiction risk	Low dopamine release, very low addiction risk

EFFICACY

(ORCA Trial Series — Achieve Life Sciences, 2019-2024)

- **ORCA (Phase 1):** No serious adverse events (AEs); most common AE was nausea (19%); maximum tolerated dose was 30 mg.
- **ORCA (Phase 2b):** 3 mg three times daily (TID) for 25 days — 30% continuous abstinence vs. 7.8% placebo at Week 4 follow-up.
- **ORCA (Phase 3):** 12 weeks of 3 mg TID outperformed both placebo and six-week duration; AEs in less than 10% of cytisinicline groups (nausea, insomnia, abnormal dreams); 3% dropout rate due to AEs.
- **ORCA V1 (vaping cessation):** 32% abstinence (cytisinicline) vs. 15% (placebo) during final four weeks of 12-week treatment.

EFFICACY OF CYTISINE VS. NICOTINE REPLACEMENT THERAPY AND VARENICLINE

Study	*n*	*Comparison*	*6-Month Abstinence*
Walker, 2014	1,310	cytisine 25 days vs. nicotine replacement therapy (NRT) 8 weeks	cytisine 22% vs. NRT 15%
Walker, 2021 (Māori)	679	cytisine 12 weeks vs. varenicline 12 weeks	cytisine 12% vs. varenicline 8%
Courtney, 2021	1,452	cytisine 25 days vs. varenicline 12 weeks	cytisine 12% vs. varenicline 13%
Oreskovic, 2023	982	cytisine 4 weeks vs. varenicline 12 weeks	cytisine 23% vs. varenicline 33%

DOSING PROTOCOL

cytisine (Tabex/cytisinicline)	*varenicline (Chantix/Champix)*
12-week treatment duration	12-week standard treatment duration, with option to extend
3 mg TID	**Days 1-3:** 0.5 mg once daily
	Days 4-7: 0.5 mg twice daily
	Days 8-84: 1 mg twice daily

ADVERSE EVENT PROFILE

Side Effect	*cytisine*	*varenicline*
Nausea	Most common Adverse Event (AE); dose-dependent; generally mild	Most common AE; take with food; generally mild
Insomnia/Abnormal Dreams	Reported in ORCA Trials 2 and 3 (less than10%); generally mild	Common; if problematic, try evening dose earlier
Neuropsychiatric (e.g., anxiety, depression, hostility)	No evidence yet; Phase 4 data pending	EAGLES Trial: no increased neuropsychiatric risk vs. placebo, including in psychiatric populations
Serious AEs (e.g., suicidal behavior)	None reported across ORCA Trial series	None identified above placebo in EAGLES

Key Takeaways:

- When taken for 12 weeks, cytisine and vareniciline show similar six-month abstinence outcomes, and cytisine outperforms NRT.
- Cytisine has side effects similar to varenicline, such as nausea and insomnia or abnormal dreams, but these effects occur in fewer people and usually are milder and more tolerable.
- Cytisine requires TID dosing, compared to twice daily (BID) dosing for bupropion or varenicline.
- Cytisine has not yet been studied in several special populations, including individuals with behavioral health conditions and people who are pregnant.

CYTISINE VS. VARENICLINE: A SHARED DECISION-MAKING GUIDE

No single agent is universally superior. The following framework supports individualized prescribing conversations.

Cost and Insurance Coverage

- As of May 2026, cytisine/cytisinicline is not yet available in the U.S., and insurance coverage is currently undefined. Providers should proactively discuss access and out-of-pocket cost with patients at the time of prescribing.
- Varenicline (generic available) is generally covered by most insurance plans and Medicare Part D. Verify formulary status for each patient.
- When cost is a barrier to varenicline, cytisine may offer a meaningful alternative — but access pathways should be confirmed before prescribing.
- Consider cytisine for patients who experienced neuropsychiatric side effects on varenicline, noting that formal safety data for cytisine context are not yet available.
- Cytisine's lower dopaminergic activity may be advantageous for patients with co-occurring substance use concerns, although direct evidence is lacking.

Patient Preference and Pill Burden

- Cytisinicline: 12-week: 3 mg TID — simpler, consistent dosing
- Varenicline: BID dosing for 12 weeks; once-daily titration phase in weeks 1-2.
- Patients who prefer a simpler schedule (no titration) may prefer cytisinicline; patients who prefer fewer pills per day may prefer varenicline.

Special Populations

Population	cytisine	varenicline
Pregnancy*	No evidence available. Use is not recommended without OB/GYN, pediatrician guidance.	Limited evidence; not associated with birth defects. Decision should be made collaboratively with OB/GYN or pediatrician.
Behavioral Health*	No dedicated behavioral health data yet. Phase 4 or targeted clinical analyses are needed before routine use can be recommended in complex psychiatric populations.	EAGLES trial: Safe in psychiatric populations with no increased neuropsychiatric risk vs. placebo. Preferred agent when behavioral health comorbidity is present.
Chronic Obstructive Pulmonary Disease (COPD)	ORCA 2 and 3 pooled analysis (Prochaska et al., 2025): Comparable efficacy in COPD vs. non-COPD patients. No heterogeneity of treatment effect.	Well-established safety and efficacy in COPD populations.

***Pregnancy and behavioral health:** Until further evidence is available, varenicline remains the preferred pharmacotherapy. These conversations should involve the patient's full care team (OB/GYN, pediatrician or psychiatrist as appropriate). Given recent analysis of empirical data, shared decision-making should center on the substantial risk of continued smoking relative to theoretical medication risk.*

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