

Cytisine: On guard at the Bastiani fortress

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Published: 31/01/2025 - DOI: <https://doi.org/10.62129/UNTT7720>

The exhaustion of existence in an absurd futility, waiting for a glorious event to justify it. In his novel, *The Tartar Steppe*, Dino Buzzatti narrates the vital tragedy of the young lieutenant Giovanni Drogo, assigned to defend a forgotten frontier, on the edge of a desertsic steppe.¹ In this metaphysical landscape arises the Bastiani fortress, an ancient bastion only sustained due to the remote possibility of a foreign attack. His time slips away as he awaits the arrival of imaginary invaders and a bronze destiny.

Cytisine was the first drug for smoking cessation in history. Its synthesis began in Bulgaria in 1964 (Tabex®), when it was part of the so-called Eastern Bloc.² With the fall of the Soviet Union, its distribution was restricted by the impossibility of conforming to European standards.³

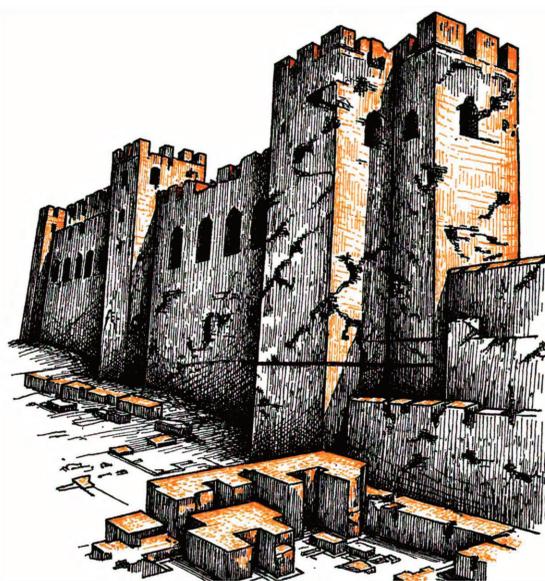
We recently published a systematic review, identifying 12 randomized controlled trials (RCT). Eight of these compared cytisine with placebo at the standard dose covering 5922 patients, 2996 of whom took cytisine, delivering a risk ratio (RR) of 2.25 [95% confidence interval (CI) = 1.42-3.56; $I^2 = 88%$] rated as moderate-quality evidence.⁴ Meta-analyses of all non-serious adverse events in the cytisine group versus placebo groups yielded a RR of 1.24 (95% CI = 1.11-1.39; studies = 8; $I^2 = 0%$; high-quality evidence).

In addition, a recent network meta-analysis (NMA) concluded that cytisine was associated with a higher smoking cessation rate at 6 months or longer, in comparison to placebo with an odds ratio (OR) of 2.21, 95% credible interval [CrI] of 1.66 to 2.97, rated as high certainty of evidence.⁵ The authors point to cytisine as the most effective intervention, along with varenicline (OR = 2.33; 95% CrI = 2.02 to 2.68) and e-cigarettes with nicotine (OR = 2.37; 95% CrI = 1.73 to 3.24) for smoking cessation, compared

to nicotinic replacement therapy (NRT), bupropion and nortriptyline.

In terms of its cost-effectiveness, an economic analysis by the National Institute for Health and Care Research (NIHR) in the United Kingdom (UK), reported that the economic model estimated more average life years and quality-adjusted years of life, and lower average living costs for treatment with cytisine than with varenicline.⁶

In July 2021, Pfizer issued a voluntary recall of twelve lots of varenicline due to nitrosamines, above the established acceptable level.⁷ Chronic exposure to N-nitroso-varenicline may be associated with an increased oncogenic risk. The U.S. Food and Drug Administration (FDA) temporarily did not oppose the marketing of generic varenicline, until the impurity could be removed or reduced.⁸ Nevertheless, varenicline is still not available in the European Union



(Credits: Meta AI)

(EU), the UK, South America, and most of North America.

In this context, cytisine constitutes an alternative of even greater relevance. However, public accessibility continues to be very limited worldwide. According to data from the World Health Organization (WHO), cytisine is only available in Azerbaijan, Bulgaria, Ivory Coast, Canada, Czechia, Georgia, Germany, Hungary, Italy, Kazakhstan, Latvia, Lithuania, Portugal, Russia, Serbia, Spain, Sweden, Ukraine, Uzbekistan and Zambia.⁹ In February 2024, through an update to the National Institute for Health and Care

Excellence (NICE) guidelines, the availability of cytisine in the UK changed, recommending its use.¹⁰

Over time, the fortress becomes ruins and oblivion, and Drogo becomes an old man without redemption, in a useless wait. Let's hope that for cytisine the end will be different.

Conflicts of interest

The authors declare no conflicts of interest.

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